Laparoscopic hysterectomy in benign gynaecological conditions

Outcomes after total laparoscopic hysterectomy and laparoscopic supracervical hysterectomy, a comparison of surgical procedures

PhD thesis by

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2. LIST OF PAPERS

Paper I:

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Paper II:

Espen Berner, Erik Qvigstad, Anne Kristina Myrvold, Marit Lieng. Pelvic Pain and Patient Satisfaction after Laparoscopic Supracervical Hysterectomy, Prospective Trial. J Minim Invasive Gynecol 2014; 21: 406-411.

Paper III:

Espen Berner, Erik Qvigstad, Anne Kristina Myrvold, Marit Lieng. Pain reduction after total laparoscopic hysterectomy and laparoscopic supracervical hysterectomy among women with dysmenorrhea: a randomised controlled trial.
British Journal of Obstetrics & Gynaecology 2014, Submitted.

3. ABBREVIATIONS

AH	Abdominal hysterectomy
AUB	Abnormal uterine bleeding
BMI	Body mass index
EFI	Endometriosis Fertility Index
FDA	U.S. Food and Drug Administration
Hb	Hemoglobin
LAVH	Laparoscopically assisted vaginal hysterectomy
LEEP	Loop electrosurgical excision procedure
LH	Laparoscopic hysterectomy
LSH	Laparoscopic supracervical hysterectomy
MIS	Minimal invasive surgery
OUS	Oslo University Hospital
POP	Pelvic organ prolapse
POP-Q	Pelvic Organ Prolapse-Quantification
Qol	Quality of life
RCT	Randomised controlled trial
SAH	Supracervical abdominal hysterectomy
SD	Standard deviation
SF-36	Short Form 36
SPSS	Statistical Package for the Social Sciences
TAH	Total abdominal hysterectomy
TLH	Total laparoscopic hysterectomy
VH	Vaginal hysterectomy
VAS	Visual analogue scale

4. SUMMARY

There has been a continued debate for decades regarding methods of hysterectomy. The disagreement has both been related to the surgical approach and the removal of cervix in women suffering from benign conditions. After the implementation of the laparoscopic approach, the rate of supracervical hysterectomy has increased. The preference of total laparoscopic hysterectomy (TLH) or laparoscopic supracervical hysterectomy (LSH) follows the corresponding discussion as for abdominal hysterectomy. Arguments in favor of LSH have been a reduced risk of complications and a more rapid recovery without compromising the long-term outcome compared to TLH. In contrast, a risk of vaginal bleeding and pelvic pain after LSH has been documented. Cervical stump symptoms after a supracervical hysterectomy might cause patient distress and repeated surgery. In addition, the risk of complication caused by tissue extraction using the morcellator during the LSH-procedure has become the focus of this debate, recently.

Inadequate amputation of the cervix during LSH may cause remnant endometrial tissue in the upper cervix. Consequently, a modification of the surgical technique might reduce the occurrence of vaginal bleeding after this procedure. For this purpose, we developed a monopolar device for a reverse loop electrosurgical excision procedure (LEEP) of the endocervix during LSH.

The risk of a persistent cyclic pelvic pain after LSH has also been recognized. Especially, this risk is evident in women with endometriosis. Therefore, various gynecologists have claimed that supracervical hysterectomy should not be performed in women with endometriosis, pelvic pain or dysmenorrhea. Other gynecologists state that endometriosis and pelvic pain should not be contraindications for performing supracervical hysterectomy, unless leaving the cervix compromises the removal of endometriosis.

In the decision of performing a total or supracervical hysterectomy in minimal invasive surgery (MIS), the benefits of LSH must be weighed up against the risk of complications and persistent cervical stump symptoms after the procedure.

Unfortunately, there is a lack of prospective randomised trials (RCT) to evaluate outcomes after different methods of MIS hysterectomy.

The persistent debate regarding methods of MIS in hysterectomy encouraged us to carry out the trials included in this PhD thesis. The aims of this thesis were to explore and compare the outcomes of different techniques of laparoscopic hysterectomy. Firstly, we intended to compare the occurrence of vaginal bleeding and patient satisfaction 12 months after LSH performed with and without the use of a reverse LEEP of the endocervix (Paper 1). Secondly, we wanted to evaluate the occurrence, intensity and reduction of cyclic pelvic pain and patient satisfaction 12 months after LSH (Paper 2). In particular, we aimed for a subgroup analysis of cyclic pelvic pain in study participants with or without perioperative detection of endometriosis and in women with or without histological confirmed adenomyosis in this trial. Finally, we wanted to compare cyclic pelvic pain, patient satisfaction and quality of life 12 months after TLH and LSH, respectively (Paper 3). An additional subgroup analysis of women with or without perioperative detection of endometriosis and in women with or without histological confirmed adenomyosis was conducted in this trial as well.

To achieve the aims mentioned above, two blinded RCTs were conducted. In addition, a prospective observational study was performed. Premenopausal women referred for hysterectomy on the basis of a benign condition were eligible for study recruitment. In the first RCT, the study participants were either allocated to the standardized LSH operative technique at our department or LSH performed with a laparoscopic LEEP of the endocervix in a reverse cone pattern. In the second RCT, the study participants were randomised to either TLH or LSH. In this RCT, the LSH was performed with the standardized operative technique without excision of the endocervix. In both RCTs, the allocated treatment was concealed for study participants throughout the 12 months follow up period. The observational trial was recruited among study participants from the first RCT and included only women with preoperative cyclic pelvic pain treated by LSH.

During planning of the trials, a power analysis for the primary outcome was conducted for each of the RCTs. The test power was set to be 90 % and the level of

significance was 0.05. In accordance to the results of the power calculations, 140 and 62 women were included in the two trials, respectively. The data of the two RCTs were analyzed according to the principle of intention to treat. The prospective observational was an open trial of women treated by LSH. Therefore, this trial was analyzed per protocol.

This PhD thesis concludes that an additional reverse LEEP of the endocervix during LSH do not reduce bleeding 12 months after the procedure compared to the standard LSH-technique. Vaginal bleeding after LSH occurs quite frequently, but the bleeding episodes are minor and do not affect patient satisfaction.

Secondly, this PhD thesis confirms a very high patient satisfaction after LSH and TLH, respectively. There is a significant and comparable improvement in Quality of life (Qol) 12 months after both procedures. There are no differences in patient satisfaction and Qol 12 months after TLH compared to LSH.

Finally, the PhD thesis demonstrates that cyclic pelvic pain is reduced to a minimum 12 months after LSH and TLH, respectively. There is no difference in cyclic pelvic pain 12 months after TLH compared to after LSH. Women with minimal, mild or moderate endometriosis detected and treated during the procedures, should anticipate the same reduction of cyclic pelvic pain 12 months after LSH or TLH compared to women without endometriosis. The same pattern should be anticipated for women with adenomyosis confirmed in the specimen from hysterectomy compared to women without adenomyosis in specimen after TLH and LSH, respectively.

The findings in this PhD will be used to individualize the preoperative counselling before MIS hysterectomy in women with benign conditions. If vaginal hysterectomy is not feasible, the laparoscopic approach is recommended. The method of LSH and TLH appears to demonstrate comparable clinical outcomes, also in women with minimal, mild or moderate endometriosis and in women with adenomyosis. If there are no documented differences in the essential outcomes in benign conditions, the safest procedure should be preferred. In addition, patient preferences must also always be taken into account. To evaluate the benefits and risks of the treatment options, an individual risk analysis should be presented to the women, preoperatively. In spite of the current recommendations, abdominal hysterectomy continues to be a

frequently used method worldwide. Compared to LSH, the TLH-technique requires more advanced laparoscopic skills. Therefore, to safely accomplish a total hysterectomy in women with fibroids, laparotomy might be the only feasible method for many gynaecologists. Consequently, to avoid laparotomy in selected women, the gynaecologist should consider performing LSH. Therefore, a more extent recommendation of LSH might reduce abdominal hysterectomy worldwide.

5. INTRODUCTION

5.1 Definitions and methods of hysterectomy

Hysterectomy is defined as removal of the uterus.[1;2] This can be performed with and without additional removal the ovaries and/or fallopian tubes. A total hysterectomy is defined as removal of the complete uterus including the cervix. In contrast, a supracervical hysterectomy is classified as removal of the uterus with preservation of the cervix. This method is also named subtotal hysterectomy or supravaginal uterus amputation.[1]

There are three major methods of conducting hysterectomy, named by their surgical approach.[1;3-5] Sometimes, a combination of two approaches is preformed. Hysterectomy has traditionally been conducted by abdominal hysterectomy (AH).[5-13] This is performed through laparotomy with midline (lower or full-length) or lower transversal (eponym: Pfannenstiel) incision. AH may be carried out as a total abdominal hysterectomy (TAH) or supracervical abdominal hysterectomy (SAH).[7;14-24] In vaginal hysterectomy (VH) the entire procedure is performed by a vaginal approach.[3-5;8;25-27] Consequently, this method leaves no visible scar on the abdomen or external genitalia. For all practical reasons, VH is only performed as a total hysterectomy. The third and most recent approach is the laparoscopic hysterectomy (LH).[3;4;9;28-34] This method is equivalent to the AH, performed laparoscopically. Therefore, LH may also be conducted as a total or supracervical hysterectomy.[28;33;35] Throughout the implementation of the laparoscopic technique the last 20 years, there have been several names and definitions of this method to distinguish the different proceedings of the LH.[2;28;33-43] The specific names rose to describe whether the entire method was performed laparoscopically or if it was conducted in a combination with VH.[2;5;9;43-46] The names and abbreviations for LH used in this thesis are total laparoscopic hysterectomy (TLH), laparoscopically assisted vaginal hysterectomy (LAVH) and laparoscopic supracervical hysterectomy (LSH). The LSH-procedure is also described in the literature as classic intrafacial supracervical hysterectomy (CISH) technique and also known by the abbreviation LASH.[37;40;47]

In this thesis, TLH is defined as the entire procedure is performed laparoscopically and the uterus is removed through the vagina. The main difference between LAVH and TLH is related to the closure of the vaginal cuff. The LAVH-procedure starts out as a laparoscopic procedure and the specimen is removed through the vagina. In LAVH, the closing of the vaginal cuff is always performed vaginally. A supplementary dissection and/or ligation of the uterine vessels may be conducted through the vaginal approach as well. For LSH, the entire procedure is performed laparoscopically. The specimen is then removed through the small incisions of the abdominal wall. After amputating the cervix during the LSH-procedure, a morcellator has often been used.[37;38;40;48-52] The morcellator is an electromechanical device designed to fragment the specimen. Thereby, the morcellator makes it possible to remove the smaller tissue through the incisions of the abdomen.

To facilitate the abdominal incisions (5-20 millimeter) in laparoscopic procedures, medical devices named trochars are used.[38;53] Normally, four incisions and trochars are used to perform a LH. The trochars are placed trans-abdominally for optimal visualization and presentation of the operating field during the procedure. The trochars are placed according to the individual preference of the operating surgeon. The typical trochar placements in LH are one in the umbilicus for use of the laparoscopic camera, one trochar in each lower quadrant of the abdomen and one placed in midline supra-pubically.[38] In recent years, flexible gel-trochars have been developed for single-incision use through the umbilicus.[53] This leaves no visual abdominal scars except for the intra-umbilical incision.

For the last decades, the robotic assisted LH has also become an option.[54-58] This procedure is classified as a variation of the laparoscopic approach, useful in selected cases. [54-58] The radical hysterectomy (eponyms: Wertheim hysterectomy or Wertheim-Meigs operation) is a last method for hysterectomy.[1] This technique is used in women suffering from oncological conditions. Therefore, this method is not covered further in this thesis of hysterectomy in benign gynecological disorders.

5.2 Clinical considerations and controversies in methods of hysterectomy

The technique for hysterectomy has been debated throughout the last century. The controversies have mostly been related to diversity in surgical approach and removal of the cervix.[2;5;8;9;13;16;17;22;24;43;59-64] In benign gynecological conditions requiring hysterectomy, there is an indisputable recommendation to use minimal invasive surgery (MIS) and thereby to avoid the AH by laparotomy.[2-5;8;63;65] If vaginal hysterectomy is not feasible, the laparoscopic approach is recommend.[3-5;9;25;28;65] However, the MIS techniques are not implemented completely. Consequently, AH continues to be frequently performed worldwide.[6;9;11-13;42;66-70]

The majority of hysterectomies include removal of the cervix, but the rate of supracervical hysterectomy has increased in women with benign conditions requiring hysterectomy.[7;10;11;21;28;35;41;67;68;71-75] There are several randomised controlled trials (RCT) comparing outcomes of total and supracervical hysterectomy.[14;17;19;21-24;28;35;76-84] Most of these RCTs compare the TAH and SAH, table 1.[14;17;19;21;23;24;77;80-82] There are only two RCTs comparing different MIS techniques of TLH, LAVH and LSH.[78;79] In addition, the trial by Thakar et al is the only RCT performed with appropriate blinding of the allocated treatment during treatment and follow up after the procedures.[24]

For the last decade, LSH has been a preferred method for hysterectomy in selected cases at our hospital.[7;31;51;85;86] This procedure is performed in premenopausal women with benign conditions and no history of previous cervical dysplasia. LSH is associated with high patient satisfaction. This procedure is easier to perform and has a lower risk of complications and faster recovery after surgery compared to TLH.[28;33;35;40;41;63;73;87-91] However, leaving the cervix during hysterectomy is debatable.[3;4;16;28;29;31;33;34;43;48-50;60;92-99] The preference of TLH or LSH follows the corresponding discussion as for AH. The incidence of cervical cancer after supracervical hysterectomy is low in countries with routine cervical screening programs. This minor risk is no justification for removal of the cervix.[22]

Table 1: Randomised controlled trials comparing total and supracervical hysterectomy techniques.

First author	Year published	n	Follow up (months)	Allocated treatments, compared
Thakar R.	2002 2009[1]	279	12 108[1]	TAH[2] versus SAH[3]
Learman L.A.	2003	135	24	TAH versus SAH
Gimbel H. Andersen L.[1]	2003 2014[1]	319	12 60[1]	TAH versus SAH
Flory N.	2006	63	6-7	LAVH[4] versus LSH[5]
Morelli M.	2007	141	24	TLH[6], versus LSH
Gorleo F.	2008	105	36	TAH versus SAH
Persson P.	2010 2013[1]	179	12 135[1]	TAH, versus SAH
Ellstrom M.A.	2010	132	12	TAH, LAVH, TLH and VH[7] versus SAH and LSH
Asnafi N.	2010	150	6	TAH, versus SAH

[1] Longterm follow up of the study population above.
[2] TAH = total abdominal hysterectomy
[3] SAH = supracervical abdominal hysterectomy
[4] LAVH = laparoscopically assisted vaginal hysterectomy
[5] LSH = laparoscopic supracervical hysterectomy
[6] TLH = total laparoscopic hysterectomy
[6] VH = vaginal hysterectomy

Several gynecologists have documented a risk of vaginal bleeding after LSH, table 2.[31;38;71;94;97;99-105] Cervical stump symptoms after this procedure might cause patient distress and repeated surgery.[31;95;97] Remnant endometrial tissue in the upper cervical canal has been claimed to be the main cause of recurrent bleeding episodes after LSH.[71] Therefore, we worked out a promising modification of the surgical technique in order to reduce the occurrence of vaginal bleeding after the procedure.[86;102] A monopolar device for reverse loop electrosurgical excision procedure (LEEP) during laparoscopy was developed. A pilot trial documented this LEEP device to be a quick and safe method for removal of the endocervix by a reverse cone during LSH.[86] No previous RCT has reported upon the impact of different

surgical LSH techniques on occurrence of vaginal bleeding and patient satisfaction following the procedure.

Table 2: Clinical trials reporting vaginal bleeding after laparoscopic supracervical hysterectomy.

First author	Year published	n	Follow up (months)	Bleeding (%)
Richards S.R.	1995	41	16	10.0
Donnez J.	1997	500	24	2.4
van der Stege J.G.	1999	20	27	25.0
Lyons T.L.	2000	236	-	1.3
Zupi E.	2001	92	24	0
Okaro O.E.	2001	70	66	11.4
Milad M.P.	2001	27	-	3.7
Ghomi A.	2005	67	3-15	19.0
Lieng M.	2005	315	36	24.0
Schmidt T.	2010	300	12	1.4-10.7
Tchartchian G.	2013	1431	6-72	23.3
Nouri K.	2013	173	36	5.2

There has also been documented a risk of persistent cyclic pelvic pain after LSH.[31;34;35;95;97;106] Especially, this risk is recognized in women with endometriosis.[31;95] Consequently, several authors have stated that supracervical hysterectomy should not be performed in women with endometriosis, pelvic pain or dysmenorrhea.[34;35;60;95;97] Even at our department, there has been a shift recent years towards TLH in women suffering from these conditions (non-published data). This alteration has occurred despite there is no high quality evidence to demonstrate a superior result for total hysterectomy compared to supracervical hysterectomy for these women.[28;35;78;79] Furthermore, some gynecologists conclude that endometriosis or pelvic pain should not be contraindications for performing supracervical hysterectomy,

unless leaving the cervix compromises the removal of endometriosis.[28;35;78;79;90;96;107;108] Therefore, in the debate of total or supracervical MIS hysterectomy, the benefits of LSH must be weighed up against the risk of complications and persistent cervical stump symptoms after the procedure.

Recently, there has also been an increasing focus on the use of the morcellator for tissue extraction during the LSH-procedure.[48-50;52;92;93;98;109-130] This has become a controversial object of discussion. Mainly, there is a concern regarding the risk of complications caused by the morcellator.[49;52;92;98;109;115;117;120;125;126] The possibility of these complications may have been underestimated, previously[48]. Firstly, there is a risk of intra-operative morcellator injury.[52;92] In addition, there is risk of retained tissue after the procedure by using the morcellator.[112;113;119;121;127;131] Finally, there is a risk of morcellating unanticipated uterine pathology including malignancy.[48-50;92;93;98;109-111;114;119;120;122-126;128;130;131] Fortunately, the complication-rate of using a morcellator is very low.[52;109] Therefore, the morcellator has been regarded a safe device to use in experienced hands for selected women after a thoroughly preoperative evaluation.[28;48;52;109]

According to the Norwegian Law for patient rights § 3.1: "The patient has the right to participate in choosing between available and medically sound methods of treatment."[132] Traditionally, the gynecologists are counseling women in choosing the appropriate method of approach and whether to preserve the cervix or not. Due to the low incidence of complications and the benefits of tissue extraction by morcellation, there is no strict routine in Norway to thoroughly inform patients of the use of morcellator or other medical devices during surgery. The gynecologist chooses the best equipment for the procedure. In contrast, complications caused by a morcellator are often severe and associated with high morbidity and increased mortality.[98;105;109;122;125] Consequently, the U.S. Food and Drug Administration (FDA) issued April 17th 2014 a safety communication where they discourage the use of laparoscopic power morcellator for fibroids during hysterectomy.[49] If a morcellator should be used during hysterectomy, the FDA instructs all health care providers in the US to inform patients that fibroids may contain unexpected cancerous tissue and that the morcellator may spread the cancer and significantly worsening their prognosis. In

addition, the FDA recommended a thorough discussion of benefits and risk of all treatments with the patients. Both, the American College of Obstetricians and Gynecologists and AAGL Advancing Minimally Invasive Gynecology Worldwide have issued thorough special reports on this topic following the FDA safety communication for the use of power morcellator.[48;50] The European Society for Gynaecological Endoscopy (ESGE) is also preparing a review paper on morcellation of fibroids.[93] Furthermore, gynaecologists worldwide are currently working to improve the LSH procedure and medical devices are developed to conduct a safe tissue extraction during LSH and myomectomy.[129;133;134]

The literature of outcomes following MIS hysterectomies mainly consists of case series and retrospective reports.[5;22;28;29;35] Therefore, there is a lack of prospective trials including women with pelvic pain, endometriosis and adenomyosis comparing outcomes after different methods of hysterectomy. Consequently, there is a need for RCTs to compare long-term clinical outcomes after these procedures.[4;22;28;35] The persistent controversies regarding methods of MIS hysterectomies encouraged us to carry out the trials included in this PhD thesis. The main objectives of surgical treatment in patients with benign conditions are through a safe method to eradicate or reduce symptoms and by this to improve the quality of life (Qol). For this reason, it is vital to evaluate patient satisfaction and Qol when outcomes of hysterectomy in women with benign gynecological conditions are studied. The objectives of the trials in this PhD thesis were to explore pelvic pain, patient satisfaction and Qol after LSH and TLH, respectively.

6. AIMS OF THE THESIS

The aim of this current thesis was to compare clinical outcomes after different LH techniques. Our first focus was to explore the cervical stump symptoms (vaginal bleeding and cyclic pelvic pain) and patient satisfaction after LSH. In addition, we wanted to compare such clinical outcomes after LSH and TLH, respectively. Furthermore, we wanted to explore outcomes of cyclic pelvic pain, patient satisfaction and Qol in women with or without endometriosis and adenomyosis.

Specifically, the aims were:

1. To compare the occurrence of vaginal bleeding and patient satisfaction 12 months after LSH performed with and without excision of the endocervix in a reverse cone pattern (Paper 1).
2. To evaluate the occurrence, intensity and reduction of cyclic pelvic pain and patient satisfaction 12 months after LSH (Paper 2).
3. To compare the occurrence, intensity and reduction of cyclic pelvic pain 12 months after TLH and LSH, respectively (Paper 3).
4. To compare patient satisfaction and quality of life 12 months after TLH and LSH, respectively (Paper 3).
5. To compare cyclic pelvic pain and patient satisfaction 12 months after TLH and LSH in women with or without perioperative detection of endometriosis and in women with or without histological confirmed adenomyosis (Paper 2 and 3).

7. MATERIALS AND METHODS

7.1 Approvals

The studies included in this PhD thesis were conducted in accordance with the Declaration of Helsinki and national as well as local regulations. The Regional Committee for Medical Research Ethics in eastern and southern Norway, the Scientific Advisory Board and the Advisory Committee on the Protection of Patient Records at Oslo University Hospital (OUS) approved the trial protocols before recruiting study participants. Written informed consent was obtained from all study participants. The studies were registered in ClinicalTrials.gov, clinical trial-identifier NCT00921778 and NCT01289314.[135]

7.2 Design

All studies included in this PhD thesis were performed as single-center trials in a gynecological department of a Norwegian university teaching hospital. We conducted two blinded RCTs. These trials were carried out and reported according to the CONSORT guidelines.[136;137] Each of the RCTs got a short title. The first RCT was named the Lapcone-trial (Paper 1). The second RCT was entitled the Lap-Hyst-trial (Paper 3). In addition, an open prospective observational trial was performed (Paper 2).

7.3 Patient selection

7.3.1 Enrollment and study populations

Premenopausal women referred to OUS for hysterectomy on the basis of a benign condition were eligible for study recruitment. The women were invited to participate and enrolled in the trials at the outpatient clinic. The authors of the studies were primarily responsible for recruiting women.

7.3.2 Inclusion / exclusion criteria

Exclusion criteria for all three trials were women unable to communicate in Norwegian language, previous history of cervical dysplasia, cellular changes suggestive of cervical dysplasia or malignancy in preoperative cervical smear or atypical hyperplasia or malignancy in preoperative endometrial biopsy. Furthermore, women with a coexisting condition requiring removal of remaining ovaries, postmenopausal women and women using hormone therapy were not included.

In addition, women who after clinical evaluation were found to benefit from vaginal, abdominal or total laparoscopic hysterectomy were not invited to participate in the trials. This exclusion criteria was more specified in the Lap-Hyst-trial. Women with pelvic organ prolapse (POP) more than grade 1 and preoperative signs of severe or deep infiltrating endometriosis or with preoperative symptoms dominated by a non-cyclic chronically pelvic pain were not invited to participate in this trial (Paper 3).[138-140] Consequently, peritoneal endometriosis or endometriosis in the pouch of Douglas was not a contraindication of being included in the trials, unless leaving the cervix compromised the removal or destruction of endometriosis. The preoperative classification of severe endometriosis was defined as presence of large endometriomas, suspected extensive adhesions or kissing ovaries due to endometriosis.[139;140]

A supplementary criterion of exclusion regarding the uterine size was added in Paper 3. Women with a substantially enlarged uterus were not included in the trial. This was defined as measurements by transvaginal ultrasound of the corpus uteri more than 10 or 12 centimeters in anterior-posterior or transversal diameter, respectively.

A fundamental criterion of inclusion in both Paper 2 and 3 was the occurrence of preoperative cyclic pelvic pain. This was defined as premenstrual pain or dysmenorrhea. The study participants in Paper 2 were recruited among women participating in the Lapcone-trial (Paper 1). Women with no preoperative cyclic pelvic pain and study participants treated with other methods of hysterectomy including all conversions to laparotomy were not included in Paper 3. Therefore, this observational trial is a per protocol analysis of women included in Paper 1 with preoperative cyclic pelvic pain treated by LSH.

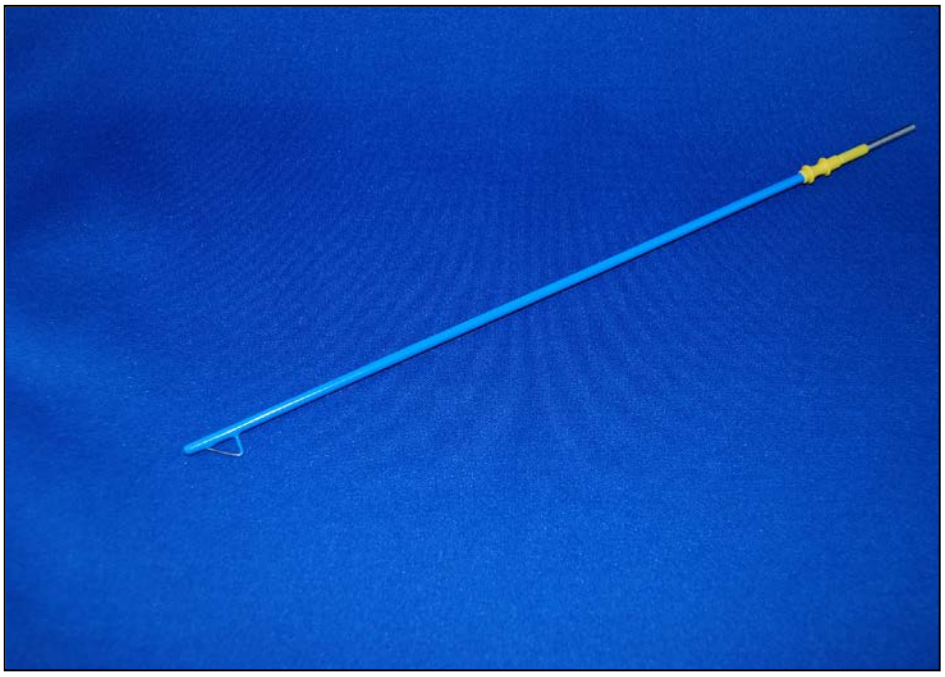
7.4 Description of interventional procedures

The study participants underwent laparoscopic hysterectomy in general anesthesia. The Pelosi Mobilizer by Apple Medical Corporation, Marlboro, MA, United States and Vcare® uterine manipulator by ConMed Endosurgery, Utica, NY, United States, were used during LSH and TLH, respectively.

In the Lapcone-trial, the study participants were either allocated to the standardized operative technique of LSH at our department or LSH performed with excision of the endocervix in a reverse cone pattern.[31;51;86] Both methods included electrocoagulation of the upper cervical canal. The excision of the endocervix was performed by a CE-approved monopolar LEEP-device by Ross Electro Medical Ltd, London, UK.[86] This device was entitled the Lapcone electrode and designed for use during laparoscopy, Figures 1a,1b and 2.

Figure 1a and 1b: Pictures of the Lapcone electrode. Lenght: 25cm, 6x10, Art. No. REM-270. The device is made by Ross Electro Medical Ltd, London, UK.

1a)



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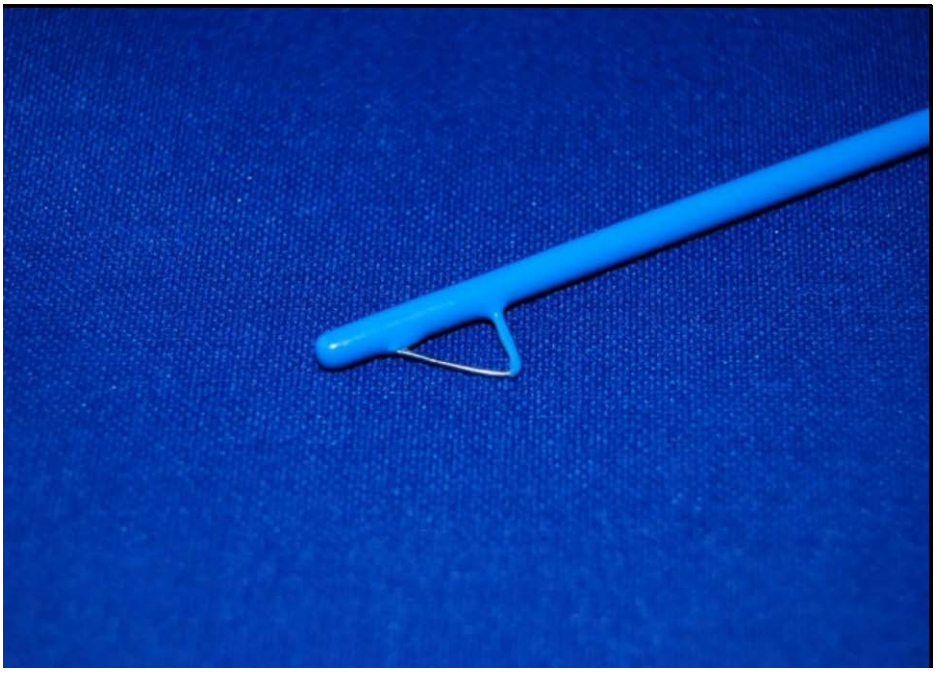
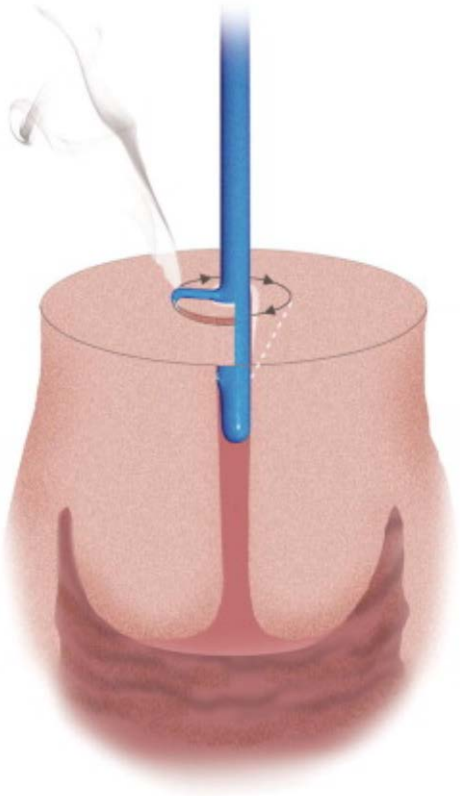


Figure 2: An illustration of conducting the excision of the endocervix by using the monopolar the Lapcone electrode, used for reverse loop electrosurgical excision procedure during laparoscopy. The illustration is made by and printed with permission from Heidi Øvergaard.



In the Lap-Hyst-trial, the study participants were randomised to either TLH or LSH. In this RCT, the LSH was performed with the standardized operative technique without excision of the endocervix.[31;51] During TLH, the surgeons individually determined the method and suture for vaginal cuff closure. This was either performed by a continuous suture of 0 (3.5 Metric) V-loc™ 180 absorbable polyglyconated or cross-sutures of 0-Polysorb, manufactured by Covidien, Dublin, Ireland. Both consultants and residents performed the LSH-procedures in the Lapcone-trial. In the Lap-Hyst-trial, six predefined endoscopic consultants performed the procedures. All study participants in the Lap-Hyst-trial received 1500-milligram of metronidazole and 400-milligram doxycycline intravenously during the procedure as a single dose of prophylactic antibiotics (Paper 3). The study participants in the Lapcone-trial did not receive prophylactic antibiotics (Paper 1 and 2). Endometriosis diagnosed perioperatively was treated during the procedure by electrocoagulation or excision.

7.5 Collection of data and outcome measures

The study participants and the primary study examiner registered most of the outcome measures at the outpatient clinic preoperatively and at follow-up 12 months after surgery. A written standardized questionnaire was used. Some outcome measures were reported through a standardized clinical interview and examination completed by the primary examiner. In addition in the Lap-Hyst-trial, the validated and well-documented Short Form 36 (SF-36) was used to evaluate Qol (Paper 3).[141]

Preoperative variables included age, body mass index (BMI), number of previous births and caesarean sections, indication for hysterectomy, any previous pelvic or abdominal surgery, medication, use of Levonorgestrel-releasing intrauterine system, other medical conditions and uterine size measured by transvaginal ultrasound (anterior-posterior diameter and width of corpus uteri).

The amount and type of vaginal bleeding (cyclic, irregular or contact bleeding) were registered both preoperatively and 12 months after surgery. This was reported in a four-graded ordinal scale (no bleeding, weak bleeding, normal bleeding or heavy

bleeding) and using a visual analogue scale (VAS), range 0-10. The occurrence and intensity of cyclic pelvic pain were registered in a four-graded ordinal scale (no pain, mild pain, moderate pain or severe pain) and a VAS (range 0-10). After hysterectomy, the cyclic pelvic pain was defined as cyclic pelvic pain with or without concomitant vaginal bleeding. The occurrence of non-cyclic chronic pelvic pain was also registered. In addition, occurrence and type of urine incontinence and occurrence of hot flashes were registered both preoperatively and 12 months after surgery. To explore potential menopause, the serum levels of Oestradiol, Follicle Stimulating Hormone, Lutein hormone were analyzed preoperatively and 12 months after hysterectomy. Additional analyzes of anti-Mullerian hormone were performed in The Lap-Hyst-trial. The patient satisfaction was reported 12 months after the procedures in an ordinal scale and a VAS (range 0-10). The length of the remaining cervix 12 months after LSH was measured by transvaginal ultrasound. In the Lap-Hyst-trial, the occurrence and type of pelvic organ prolapse (POP) defined by Pelvic Organ Prolapse-Quantification (POP-Q) was registered both preoperatively and 12 months after surgery.[138] Additional variables 12 months after hysterectomy were return to normal activity (days) and any new symptoms.

A scrub-nurse recorded the perioperative variables (operation time, weight of specimen, perioperative complications and estimated blood loss). The nurses at the gynecological ward registered body temperature, length of stay and complications before discharge from the hospital. All further contacts (re-consultations and readmissions) and complications during the 12-month follow-up were continuously reported to the primary investigator.

In all trials, preoperative cervical cytology and endometrial biopsy, histological analysis of specimen from the surgical procedure and cervical cytology 12 months after surgery were registered. A dedicated pathologist analyzed all specimens with a 2.0 millimeters dept of invasion of endometrial glands below the basalis layer as diagnostic cutoff criteria for adenomyosis.

7.6 Randomisation and concealed allocated treatment

In the two RCTs, a full randomisation at a ratio of 1:1 was performed using the randomisation plan generator with permuted blocks.[142] A study nurse, not otherwise involved in the study, performed the randomisation procedure. The treatment assignment was concealed in numbered envelopes stored in the operating theatre. The study nurse and a senior supervisor of the trials kept a code list with the concealed allocated treatments throughout the follow-up period 12 months after the procedures.

In the Lapcone-trial, the allocated treatment was revealed for the surgeon after amputation of the cervix, and the assigned intervention performed. The surgeon documented the following description in the medical record: “The LSH was performed according to the allocated treatment in the Lapcone-trial”. Consequently, the allocated treatment was blinded both for the study participants and for the primary examiner at follow-up consultations. The primary examiner got access to the code list after all outcome variables were registered in an internal research database. The study participants were informed of the allocated treatment after the follow-up consultation 12 months after LSH.

In the Lap-Hyst-trial, the envelope was not opened until general anaesthesia of the study participant was established. To ensure good medical care, a description of the allocated treatment (TLH or LSH) was registered in the medical chart. In order to increase the validity of the trial, the assigned procedure was kept blinded for the study participants throughout the follow-up period. In the Lap-Hyst trial, the primary examiner and study participants were informed of allocated treatment after completing the study forms at follow up 12 months after hysterectomy.

7.7 Statistics

7.7.1 Test power

Power analyses were conducted before commencing the RCTs. The test power and level of significance in both trials were set to 90 % and 0.05, respectively.

In the Lapcone-trial, there was an expected occurrence of vaginal bleeding in 24 % after LSH for women treated by the standard procedure.[31] A reduction in occurrence of vaginal bleeding from 24 % to 5 % was considered clinically significant. The number of women required was calculated to be 140.

For participating women in The Lap-Hyst-trial, the expected mean of cyclic pelvic pain reduction treated by LSH was 3.3 with a standard deviation (SD) of 2.7.[31] During planning of the trial, there was no available data for the expected reduction of pain after TLH. A difference in pelvic pain reduction between LSH and TLH equal to 1 SD was considered to be of clinical importance. Consequently, 62 women were required in the trial.

7.7.2 Statistical analysis

In the two RCTs, data were analyzed according to the principle of intention to treat. An additional analysis per protocol was performed if there were any deviations in the treatment or follow-up. The prospective observational study was an open trial of women treated by LSH. Therefore, this trial was analyzed per protocol.

All statistical tests were two-sided and p= 0.05 was considered statistical significant. The statistical analyses were performed using commercial available software (SPSS version 15.0 and 18.0, SPSS, Inc., Chicago, IL). Normally distributed continuous data from two study groups were analyzed using a two-sided Independent Samples Student t-test and the Paired Samples t-test when paired. For non-normally distributed data, the Mann-Whitney U test and Wilcoxon Signed Rank Test were used. Categorical data were analyzed using Pearson Chi-Square.

7.8 Ethics

Before recruiting study participants, The Regional Committee for Medical Research Ethics in eastern and southern Norway approved trial protocols. A pilot-study had been performed during planning of the first RCT. This validated the Lapcone electrode as a safe and quick method for removal of the endocervix in a reverse cone during LSH.[86] Therefore, the trial protocol for the Lapcone-trial was approved without major annotations (Paper 1 and 2).

In contrast, there were some necessary ethical considerations regarding conducting of the Lap-Hyst-trial (Paper 3). This was mainly related to the concealment of the allocated treatment throughout the follow-up period of 12 months after the procedures. According to the study protocol, the study participants should not be informed whether cervix was preserved or not during hysterectomy during the follow up periode. According to the Norwegian Law for patient rights (Norwegian: Lov om pasient- og brukerrettigheter) § 3.2 *The patient`s right to information* "The patient shall have the information that is necessary to obtain an insight to his or her health condition and the content of health care".[132] To achieve this and the appropriate ethical approval of the study design, the following statement was included in the information (in Norwegian) given to women eligible for study recruitment when they were invited to participate and enrolled in the trial: "If complications related to the allocated treatment occur, study participants will obtain information regarding allocated treatment. If study participants for other reasons wish to obtain information of allocated treatment performed, she has the right to access her medical records to get such information, according to Law for patient rights §3-2."

8. SUMMARY OF RESULTS

8.1 Laparoscopic Supracervical Hysterectomy Performed With and Without Excision of the Endocervix: A Randomized Controlled Trial. (Paper 1)

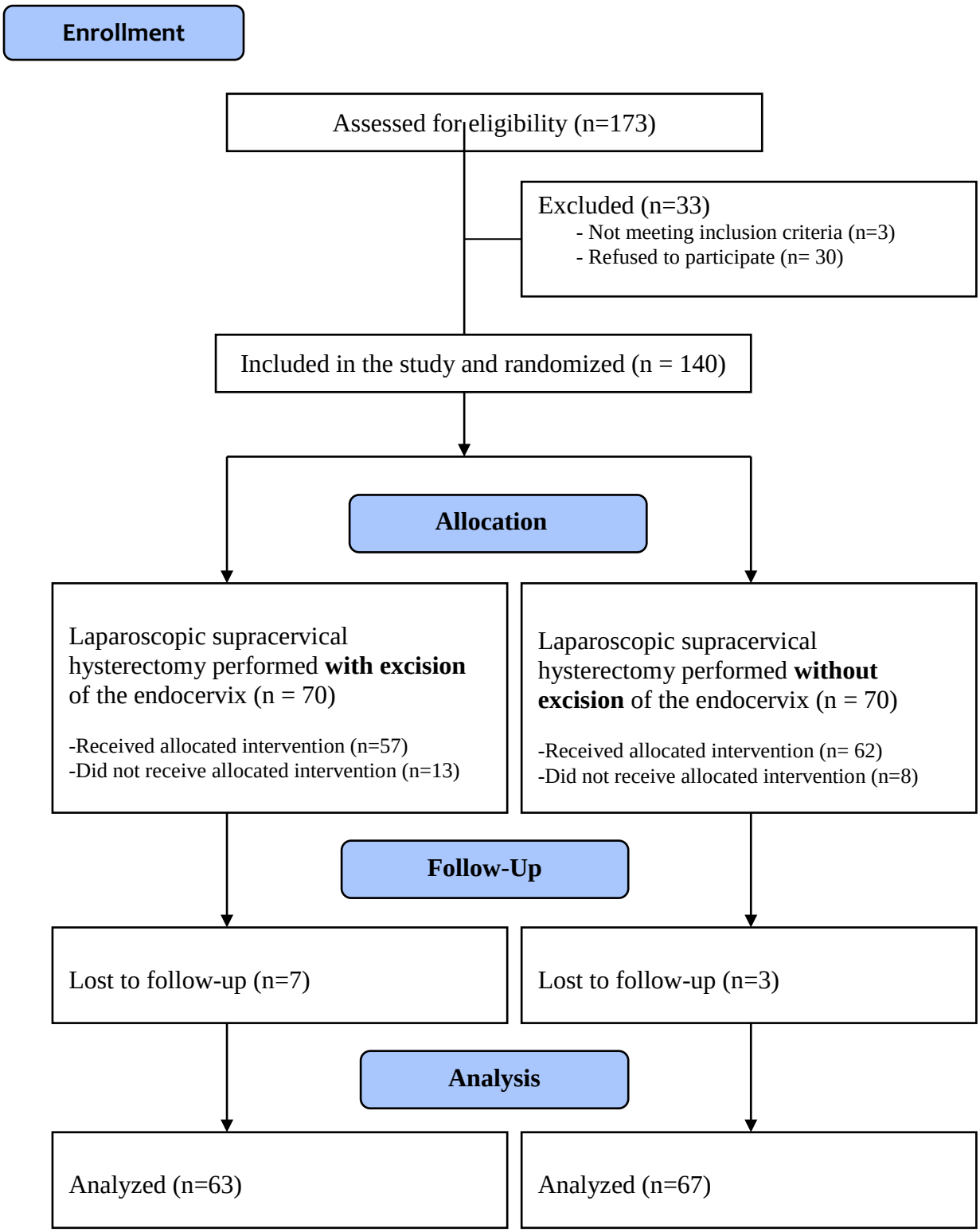
A total of 140 women were randomised to standard laparoscopic supracervical hysterectomy (n = 70) or laparoscopic supracervical hysterectomy with excision of the endocervix in a reverse cone pattern (n = 70). They were followed up according to the study protocol (Figure 3). There were no differences between the two allocated treatment groups in preoperative demographic data and perioperative variables. We found no difference in occurrence of vaginal bleeding or patient satisfaction 12 months after the procedures (table 3). For all study participants, the mean amount of vaginal bleeding was reduced from 7.4 (SD 2.4) preoperatively to 0.2 (SD 0.4) 12 months after LSH measured by VAS ($p<0.01$). The mean patient satisfaction was 9.0 (SD 1.9) measured by VAS in women with bleeding 12 months after LSH compared to 9.4 (SD 1.2) for women without bleeding after surgery, $p= 0.15$. Among women treated by excision of the endocervix (n=59), endometrial tissue was detected in seven (12.7%) specimens of the removed cones. The mean length of the remaining cervix measured by transvaginal ultrasound was 2.7 cm (SD 0.6). The length of the cervix did neither affect the occurrence of endometrial tissue in the endocervical-cones nor vaginal bleeding after LSH.

Table 3**.** Outcomes of vaginal bleeding and patient satisfaction 12 months after Laparoscopic supracervical hysterectomy in both treatment groups. (Paper I)

Outcomes 12 months after LSH[1]	**LSH performed without excision of the endocervix (n=67)[1]**	**LSH performed with excision of the endocervix (n=63)[1]**	**p-value**
No bleeding episodes, n (%)	45 (67.2)	42 (66.7)	0.95
Regular bleeding,n (%)	11 (16.4)	11 (18.0)	0.99
Irregular bleeding episodes, n (%)	11 (16.4)	10 (15.9)	0.99
Amount of bleeding, (VAS), mean (SD)[2]	0.2 (0.4)	0.3 (0.5)	0.35
Patient satisfaction (VAS), mean (SD)[2]	9.3 (1.4)	9.2 (1.5)	0.73

[1] Laparoscopic supracervical hysterectomy (LSH)
[2] Visual analogue scale (VAS), range 0-10

Figure 3: Study flow chart Paper 1.



8.2 Pelvic Pain and Patient Satisfaction after Laparoscopic Supracervical Hysterectomy, Prospective Trial. (Paper 2)

A total of 113 women with preoperative cyclic pelvic pain and treated by LSH were included in the trial. Eight women (7.1%) were lost to follow up. Endometriosis was detected perioperatively in 14 (%) study participants. After LSH, adenomyosis was found in 19 (18.1%) of the specimens.

The occurrence of cyclic pelvic pain was reduced to a minimum 12 months after the procedure, $p < .01$ (table 4). The mean intensity of cyclic pelvic pain was reduced from 5.5 (SD 2.4) preoperatively to 0.7 (SD 1.5) measured by VAS 12 months after LSH, $p < 0.01$. There was no difference in mean reduction of cyclic pelvic pain among women with adenomyosis compared with women without adenomyosis measured by VAS, $p= 0.45$. The mean patient satisfaction for women with and without adenomyosis was 9.5 (SD 1.3) and 9.2 (SD 1.5) measured by VAS, respectively ($p= 0.24$). Women with endometriosis reported a higher intensity of cyclic pelvic pain preoperatively compared to women with no signs of endometriosis during LSH, $p=0.05$. There was no difference in reduction of cyclic pelvic pain 12 months after the procedure in women with or without a perioperative detection of endometriosis, $p=0.60$. The mean patient satisfaction measured by VAS 12 months after LSH for women with or without perioperative detection of endometriosis was 9.3 (SD 1.5) and 9.3 (SD 1.7), respectively ($p= 0.9$). The length of the remaining cervix after LSH (mean 2.7 cm, SD 0.6) did not appear to influence the occurrence or intensity of pelvic pain 12 months after the procedure.

Table 4: Cyclic pelvic pain among study participants in the trial with complete follow-up by an ordinal and visual analogue scale. The scores are reported preoperatively and 12 months after laparoscopic supracervical hysterectomy. The table is for subgroups of women with and without adenomyosis and endometriosis, respectively. (Paper II)

Cyclic pelvic pain		**Adenomyosis[2]**		**Endometriosis[3]**	
		Adenomyosis detected (n = 19)	No Adenomyosis (n = 86)	Endometriosis detected (n = 14)	No Endometriosis (n = 91)
Preoperatively	Weak pelvic pain, n (%)	4 (21.1)	28 (32.6)	0 (0.0)	32 (35.2)
	Moderate pelvic pain, n (%)	7 (36.8)	39 (45.3)	9 (64.3)	37 (40.7)
	Severe pelvic pain, n (%)	8 (42.1)	19 (22.1)	5 (35.7)	22 (24.2)
	Pelvic pain, mean VAS (SD)[4]	**6.3 (2.7)**	**5.4 (2.3)**	**6.4 (1.8)**	**5.3 (2.6)**
12 months after LSH[1]	No pelvic pain, n (%)	12 (63.2)	59 (68.6)	10 (71.4)	62 (68.1)
	Weak pelvic pain, n (%)	4 (21.1)	23 (26.7)	2 (14.3)	24 (26.4)
	Moderate pelvic pain, n (%)	2 (10.5)	4 (4.7)	1 (7.1)	5 (5.5)
	Severe pelvic pain, n (%)	1 (5.3)	0 (0.0)	1 (7.1)	0 (0.0)
	Pelvic pain, mean VAS (SD)[4]	**1.0 (2.0)**	**0.6 (1.4)**	**1.2 (2.6)**	**0.6 (1.3)**

[1] Laparoscopic supracervical hysterectomy (LSH).
[2] Adenomyosis detected in specimen from operation.
[3] Endometriosis detected perioperatively.
[4] Visual analogue scale (VAS), range 0-10.

8.3 Pain reduction after total laparoscopic hysterectomy and laparoscopic supracervical hysterectomy among women with dysmenorrhea: a randomised controlled trial. (Paper 3)

In total, 62 women were included in the trial. They were followed-up according to the study flow chart, figure 4. The preoperative demographic variables and intensity of cyclic pelvic pain were comparable for the two allocated treatment groups. The mean duration of surgery in the LSH-group was 76.0 (SD 25.1) minutes compared to 102.7 (SD 27.3) for TLH, p=0.01.

Figure 4: Study flow chart Paper 3.

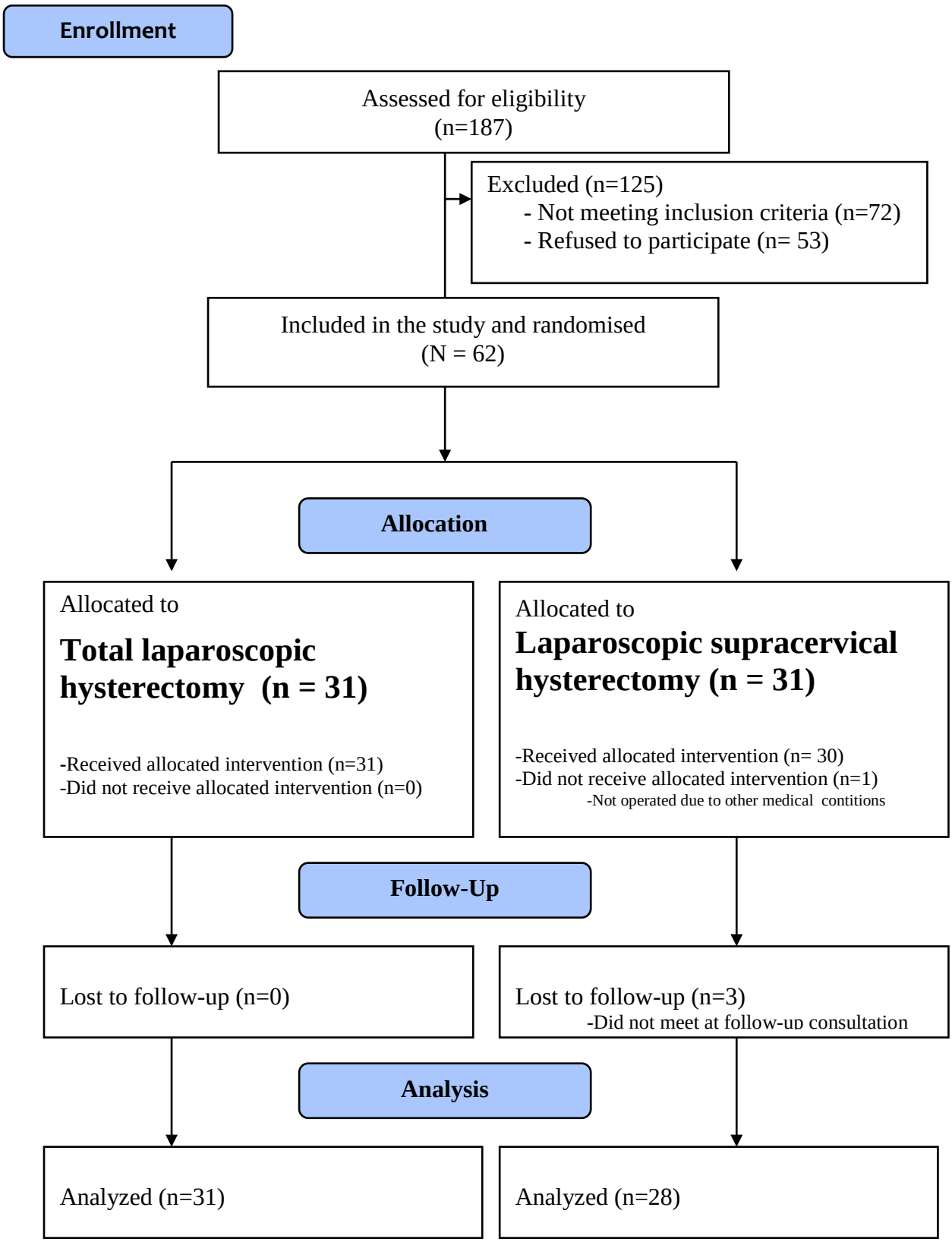


Table 5: Outcome measures in the allocated treatment groups 12 months after hysterectomy. (Paper 3)

	TLH[1] (n=31)	**LSH[2] (n=28)**	**p-value**
Cyclic pelvic pain reduction (VAS), mean (SD)[3,4]	5.8 (2.6)	6.0 (2.6)	0.77
Cyclic pelvic pain 12 months after hysterectomy (VAS), mean (SD)[3]	0.8 (1.6)	0.8 (2.0)	0.94
Cyclic pelvic pain 12 months after hysterectomy, n (%)	10 (32.3)	7 (25.0)	0.54
Patient satisfaction 12 months after hysterectomy, mean VAS (SD)[3]	9.3 (1.5)	9.1 (1.2)	0.43
Qol 12 months after hysterectomy (SF-36, total score), mean (SD)[5]	81.6 (17.8)	80.2 (18.0)	0.69
Qol (SF-36, total score) improvement, mean (SD)[5,6]	17.6 (20.0)	13.9 (26.0)	0.56
Pelvic organ prolapse 12 months after hysterectomy, n (%)[7]	10 (32.3)	5 (17.8)	0.23
Occurrence of vaginal bleeding 12 months after hysterectomy, n (%)[8]	3 (9.7)	9 (32.1)	0.03

[1] Total laparoscopic hysterectomy (TLH).
[2] Laparoscopic supracervical hysterectomy (LSH).
[3] Visual analogue scale (VAS) Range 0-10.
[4] Cyclic pelvic pain reduction: The VAS preoperatively minus VAS 12 months after surgery.
[5] Quality of life (Qol) by Short form 36 (SF-36) Range 0-100. A total score is reported if all questions of SF-36 are completed.
[6] Qol improvement: SF-36-score 12 months after surgery minus SF-36-score preoperatively.
[7] Pelvic organ prolapse (POP) 12 months after hysterectomy by POP-Quantification, all grade 1.
[8] All bleeding episodes were minor, both cyclic and irregular bleeding reported. Irregular bleeding episodes reported in the allocated treatment groups: TLH (n=3) and LSH (n=5).

The mean reduction of cyclic pelvic pain 12 months after TLH and LSH measured by VAS 0-10 was 5.8 (SD 2.6) and 6.0 (2.6), respectively (p= 0.77) (table 5). There were no differences between the two allocated treatment groups in occurrence and intensity of cyclic pelvic pain, patient satisfaction or Qol 12 months after hysterectomy, (p=0.54, p=0.94, p=0.43, p=0.69) respectively. The patientsatisfaction measured by VAS after TLH and LSH was 9.3 (SD 1.5) and 9.1

(SD 1.2), respectively. The mean Qol scores 12 months after hysterectomy measured by SF-36 were higher for all study participants and for both allocated treatment groups separately compared to the preoperative values, ($p<0.02$) respectively.

Women with endometriosis (n=15) reported the same intensity of preoperative cyclic pelvic pain compared to women without endometriosis (n=46), p= 0.89 (table 6). The reduction of cyclic pelvic pain 12 months after hysterectomy measured by VAS for women with and without endometriosis was 5.8 (SD 2.2) and 5.9 (SD 2.6), respectively. In contrast, study participants with adenomyosis (n=27) reported higher preoperative cyclic pelvic pain (mean 7.7, SD 1.6) compared to women without this diagnosis (n=34) (mean 6.0, SD 2.4), p=0.03. Furthermore, there was a tendency of a greater pelvic pain reduction in women with adenomyosis (mean 6.5, SD 2.3) compared to women without this diagnosis (mean 5.3, SD 2.6), p=0.06. There was no significant difference in intensity of cyclic pelvic pain in women with or without adenomyosis 12 months after hysterectomy, p=0.23. The mean patient satisfaction 12 months after hysterectomy for women with or without endometriosis was 9.2 (SD 0.6) and 9.2 (SD 1.5), respectively (p=0.99). The corresponding figures for women with or without adenomyosis were 9.1 (SD 1.7) and 9.3 (SD 0.9), respectively (p=0.55). There were similar improvements in Qol scores for women with endometriosis and adenomyosis compared to women without these conditions, $p>0.1$.

The women returned to normal activity after LSH and TLH within mean 25.8 (SD 11.9) and 35.8 (SD 26.8) days, respectively (p=0.15). There was a trend towards more re-consultations after discharge from the hospital in the TLH-group (n=11), compared to the women who were treated with LSH (n=5), p=0.08. As expected, we found a higher occurrence of vaginal bleeding after LSH compared to TLH, p=0.05. The occurrence of vaginal bleeding did neither affect patient satisfaction nor Qol 12 months after hysterectomy.

Table 6: Outcome measures 12 months after hysterectomy in the allocated treatment groups for women with and without endometriosis or adenomyosis, respectively. (Paper 3)

		TLH[1] (n=31)	LSH[2] (n=30)	p-value
ENDOMETRIOS	**No endometriosis detected during surgery, n (%)**	**24 (77.4)**	**22 (73.3)**	**0.71**
	Reduction of cyclic pelvic pain (VAS), mean (SD) [3,4]	5.8 (2.6)	5.9 (2.7)	0.89
	Cyclic pelvic pain (VAS) 12 months after hysterectomy, mean (SD) [3]	0.8 (1.6)	0.8 (2.3)	0.98
	Patient satisfaction (VAS) 12 months after hysterectomy, mean (SD) [3]	9.3 (1.6)	9.2 (1.4)	0.86
	Qol (SF-36, total score) 12 months after hysterectomy, mean (SD)[5]	83.2 (17.2)	82.1 (17.3)	0.82
	Endometriosis detected and treated during surgery, n (%)	**7 (22.6)**	**8 (26.7)**	**0.71**
	Reduction of cyclic pelvic pain (VAS), mean (SD) [3,4]	5.6 (2.8)	6.1 (1.5)	0.71
	Cyclic pelvic pain (VAS) 12 months after hysterectomy, mean (SD) [3]	1.0 (1.5)	0.8 (1.4)	0.82
	Patient satisfaction (VAS) 12 months after hysterectomy, mean (SD) [3]	9.4 (0.5)	9.0 (0.7)	0.26
	Qol (SF-36, total score) 12 months after hysterectomy, mean (SD)[5]	78.8 (20.5)	74.0 (20.2)	0.68
ADENOMYOSIS	**No adenomyosis in specimen from hysterectomy, n (%)**	**16 (51.6)**	**18 (60.0)**	**0.51**
	Reduction of cyclic pelvic pain (VAS), mean (SD) [3,4]	4.9 (2.6)	5.7 (2.6)	0.44
	Cyclic pelvic pain (VAS) 12 months after hysterectomy, mean (SD) [3]	0.5 (1.2)	0.6 (2.1)	0.93
	Patient satisfaction (VAS) 12 months after hysterectomy, mean (SD) [3]	9.5 (0.6)	9.1 (1.1)	0.22
	Qol (SF-36, total score) 12 months after hysterectomy, mean (SD)[5]	83.6 (16.0)	78.6 (17.1)	0.41
	Adenomyosis detected in specimen from hysterectomy, n (%)	**15 (48.4)**	**12 (40.0)**	**0.51**
	Reduction of cyclic pelvic pain (VAS), mean (SD) [3,4]	6.6 (2.4)	6.4 (2.2)	0.74
	Cyclic pelvic pain (VAS) 12 months after hysterectomy, mean (SD) [3]	1.2 (1.8)	1.1 (2.1)	0.94
	Patient satisfaction (VAS) 12 months after hysterectomy, mean (SD)[3]	9.1 (2.0)	9.2 (1.4)	0.88
	Qol (SF-36, total score) 12 months after hysterectomy, mean (SD)[5]	80.6 (20.0)	82.4 (19.6)	0.82

[1] Total laparoscopic hysterectomy (TLH).
[2] Laparoscopic supracervical hysterectomy (LSH).
[3] Visual analogue scale (VAS), Range 0-10.
[4] Cyclic pelvic pain reduction: preoperative VAS-score minus VAS-score 12 months after surgery.
[5] Quality of life (Qol) by Short form 36 (SF-36), Range 0-100. A total score is reported if all questions of SF-36 are completed.

8.4 A comparison of the trials in the PhD thesis

In general, the preoperative demographic data and symptoms of study participants in the Lapcone-trial and the Lap-Hyst-trial were comparable, table 7. The study participants in the Lapcone-trial were included and procedures were performed in the period 09/2008 – 09/2010. The Lap-Hyst-trial was conducted in the period 02/2011 – 11/2012 and followed up for 12 months after the procedures.

There were no differences in the main indications for hysterectomy between the two RCTs. The preoperative size of uterus and weight of specimen removed during hysterectomy were higher in the Lapcone-trial compared to the Lap-Hyst-trial, $p<0.05$.

The mean duration of surgery in the Lapcone-trial was 98.5 (SD 35.6) minutes compared to 89.5 (SD 29.3) minutes in the Lap-Hyst-trial, $p=0.07$. If only the LSH procedures in the two trials were calculated, the mean time of operation in the Lapcone-trial (n=124) was 96.5 (SD 35.5) compared to 76.0 (SD 25.2) in the Lapcone trial (n=30), $p=0.01$. There was a higher incidence of endometriosis detected during surgery and adenomyosis identified in the specimen after hysterectomy in the Lap-Hyst-trial compared to women participating the Lapcone-trial, respectively ($p<0.05$).

Finally, there was a higher incidence of complications in the Lapcone-trial compared to the Lap-Hyst-trial, $p<0.05$. Mainly, minor complications occured. Converson to laparotomy (n=3) was registered as a minor complication in the Lapcone-trial. Among all women in this Ph.d thesis, five major complications occurred. One women who underwent LSH with excision of severe endometriosis detected perioperatively in the Lapcone-trial had an intra abdominal hematoma requiring surgical drainage 12 days after the procedure. The second major complication in this trial was an injury of the urine bladder in a woman with two previous caesarean sections. The injury was detected within 24 hours after the LSH, and a re-operation with laparoscopic suturing of the urine bladder was performed. For one woman in the Lap-Hyst trial, an infected cervical top hematoma was diagnosed and successfully treated with antibiotics three weeks after LSH. Two women in this trial experienced vaginal dehiscence three and six months after TLH, respectively. They were both re-operated with laparoscopic suture of the vaginal cuff.

Table 7: A comparison between the Lapcone-trial and the Lap-Hyst-trial. The trial period, preoperative demographic data, indication for hysterectomy, preoperative symptoms and measures, perioperative variables, histological diagnosis and complications in both trials.

Variables	**The Lapcone-trial (n=140)**	**The Lap-Hyst-trial (n=62)**	**p-value**
Trial period of inclusion and hysterectomy	09/2008 - - 09/2010	02/2011 - - 11/2012	-
Preoperative demographic data			
Age (years), mean (SD)	44.2 (4.8)	44.8 (4.9)	0.62
Body mass index, mean (SD)	25.2 (4.9)	26.2 (5.6)	0.71
Main indication for hysterectomy			
Fibroids, n (%)	73 (64.6)	39 (62.9)	-
AUB, n (%)	27 (23.9)	14 (22.6)	-
Dysmenorrea, n (%)	13 (11.5)	9 (14.5)	-
Preoperative symptoms and measures			
Vaginal bleeding (VAS), mean (SD)[1]	7.5 (2.3)	7.9 (1.8)	0.29
Cyclic pelvic pain (VAS), mean (SD)[1,2]	5.5(2.6)[2]	6.7 (2.2)	0.01
Uterine size transversal (cm), mean (SD)[3]	8.5 (9.5)	6.9 (1.3)	0.11
Uterine size AP (cm), mean (SD)[3]	7.8 (9.0)	5.8 (1.3)	0.04
Perioperative variables and histological diagnosis			
Duration of surgery (minutes), mean (SD)[4]	98.5 (35.6)	89.5 (29.3)	0.07
Weight of specimen (gram), mean (SD)	299.5 (271.3)	187.3 (93.7)	0.01
Endometriosis detected during surgery, n (%)[5]	12 (12.4)	15 (24.6)	0.04
Adenomyosis in specimen, n (%)[6]	19 (16.7)	27 (44.3)	0.01
Histology sections examined in specimen, mean (SD)[6]	5.5 (1.7)	5.8 (2.0)	0.87
Surgeons performed hysterectomy in the trial, n[7]	28	6	0.05
Complications			
Total, peri- and postoperative complications, n (%)	25 (17.9)	6 (9.8)	0.05
Minor complications, n (%)	23 (16.4)	3 (4.9)	-
Major complications, n (%)	2 (1.4)	3 (4.9)	-

[1] Measured by visual analogue scale (VAS), range 0-10. [2] There were 16 women without cyclic pelvic pain in the Lapcone-trial. The results reported in this table is the result of women in the observational trial, recruited among women with cyclic pelvic pain treated by LSH. [3] Measured by vaginal ultrasound, transversal and anterior-posterior (AP) diameter of the corpus uteri. [4] Time from application of the uterine manipulator until completed skin closure. [5] Endometriosis diagnosed during surgery was treated by electrocoagulation or excision. [6] Histological diagnosis of specimen from operation. Sub-group analysis of The Lap-Hyst-trial: adenomyosis was diagnosed in n=15 (48.4 %) and n=12 (44.0%) in the TLH and LSH-group, respectively (p=0.51) [7] Selected endoscopic consultants (n=6) performed all procedures in The Lap-Hyst-trial. Both consultants (n=12) and residents (n=16) performed the procedures in The Lapcone-trial.

9. DISCUSSION

9.1 Patient selection

The study participants included in this PhD thesis were recruited among premenopausal women referred to the department of gynaecology OUS due to a benign condition requiring hysterectomy. Our department also offers a high amount of minimally invasive uterus-sparing treatment options. Hysteroscopic endometrial resection and hysteroscopic resection of fibroids (< 3.5 cm in diameter) are widely performed.[143] Uterine artery embolization and myomectomy is also an option in selected cases.[49;144-146] Thereby, other procedures are often recommended as alternatives to hysterectomy.[143;144;146] Therefore in our department, the uterus is often significant enlarged when hysterectomy for a benign condition is performed. Our standard practice is to recommend VH as treatment of choice in women with a normal sized or slightly enlarged uterus (uterus size correspond to <9 weeks of pregnancy). If there is further enlargement of the uterus and for women with endometriosis, the laparoscopic approach is offered. Consequently, mainly women with an enlarged uterus due to fibroids were included in the trials.

In Paper 3 there was a strict criterion of inclusion regarding the maximum size of the uterus. In contrast, there was no exclusion criterion in the size of uterus in Paper 1 and 2. The diversity in criteria of inclusion may have caused the difference in outcomes such as preoperative size of uterus, weight of specimen and operating time in the two RCTs. Furthermore, at the time we planned and conducted study 1, our department had no predefined limits regarding the size of uterus when offering LSH as an option. There was an attitude to offer the laparoscopic approach to the highest degree of women referred to hysterectomy. Thereby, the feasibility and boundaries of the laparoscopic approach were tested out. If a perioperative risk of safety by conducting the LSH-procedure occurred, a conversion to laparotomy was carried out. This approach has probably influenced the incidence of conversion to laparotomy in Paper 1. In 2010, the criteria for LSH in our department were modified. We currently recommend abdominal hysterectomy for women with an enlargement of uterus that correspond to >15 weeks of pregnancy. Consequently, we offer MIS hysterectomy to

women when we are convinced this method is feasible without increasing the risk of intra-operative complications.

Study participants in the Lapcone trial were included among women referred and planned for LSH. The primary examiner of the trial did not overrule a recommendation for LSH given by a consultants in the department. A difference in preoperative evaluation among gynecologists might explain the heterogeneity of women included in the Lapcone-trial. In contrast, the first author recruited all the study participants in the Lap-Hyst-trial. In this trial, the inclusion/exclusion criteria were more strictly defined. The preoperative evaluation of symptoms and clinical findings of study participants in this trial were homogeneous compared to the study participants in the Lapcone-trial. Consequently, the population studied in Paper 3 was more selected. The study participants in Paper 1 represent a general population of women planned for LSH at the time this trial was conducted.

The RCTs conducted were designed with concealment of the allocated treatment during the follow-up of 12 months. This concealment was the major reason for refusal to participate in the Lap-Hyst-trial. Except for the excision of the endocervix, the allocated procedures offered in study 1 were to a large extent the same. The minor difference between the procedures in this trial may have caused fewer refusals to participate in this trial compared to the Lap-Hyst-trial.

9.2 Methodological considerations

9.2.1 Study design

The design of the two RCTs ensured a strong external validity for the primary outcome of the trials. Especiallly, the blinding of the allocated treatment throughout 12 months follow-up after the procedures improved the quality of these trials.

Some methodological weaknesses need to be acknowledged. The lack of reference group in Paper 2 weakens the conclusion of this prospective observational trial. In addition, the number of study participants is the main limitation of the trials included in this PhD thesis. Consequently, results of subgroup analyzes in the trials must be interpreted with caution. To estimate the number of women needed for the main outcome of the RCTs, power analyses were performed. The prevalence of

endometriosis and adenomyosis is reported in a wide range (20-60 %) in different studies of hysterectomy.[131;147-150] If the trials should have been powered for sub-group analysis of endometriosis and adenomyosis, additional pilot studies and supplementary power analyses should have been performed. This would probably have concluded with requirement of a substantially larger study population in both of the trials if subgroup analyses with adequate power and level of significance for these conditions should have been conducted. It is both costly and time-consuming to conduct an even larger high-quality RCT comparing different methods of hysterectomies. This was not achievable within the granted recourses available for this PhD thesis.

9.2.2 Outcome measures

Most outcome measures in all three trials were subjective. The use of a more accurate method for assessment of periodic blood loss, such as the alkaline hematin method, may have improved the quality of Paper 1.[151] However, although this method is more reliable than a VAS, it requires that the study participants hand in all soiled sanitary pads and tampons to the study investigator. Consequently, we feared that this method would have made study recruitment difficult and follow-up more challenging. Clinical evaluations in response of treatment in benign conditions are usually based on subjective perception of symptoms. Therefore, the measurements used in our studies reflect the foundation most commonly used for clinical decisions.

The VAS was used to measure the severity of vaginal bleeding, patient satisfaction and cyclic pelvic pain in the trials. This scale is widely used in clinical practice for evaluation of treatment. The VAS is validated for use in gynecological conditions and for recall pain.[152] This scale is a continuous variable and does not force study participants into fixed categories. Therefore, the scale can be used for parametric statistical analysis.

Both Paper 1 and 2 had profited on an additional variable evaluating the Qol. Therefore, this outcome was added during planning of Paper 3. In this trial, we used the SF-36.[141] This is a well-documented Qol-scale. The Uterine Fibroid Symptom and Quality of Life questionnaire is more specific for gynecological symptoms.[153] In contrast, there is no consensus of which validated Qol-scale that should be preferred

for trials evaluating outcomes following hysterectomy. In addition, the trials had most likely improved if we had explored outcome of endometriosis using a validated endometriosis-scale like the Endometriosis Fertility Index (EFI) or ENZIAN score.[139;140;154] Unfortunately, these scales were not systematically used in clinical practice in our department at the time we conducted the trial. The EFI and EZIAN score are used to evaluate the peri-operative severity of endometriosis. The definition of severe endometriosis used in our trials ensured the preoperative detection of severe endometriosis by a clinical examination and vaginal ultrasound, preoperatively. Therefore, the scales were not necessary for correct inclusion in the trials.

Furthermore, to make a correct diagnosis of adenomyosis in the specimen after morcellation is debatable.[115;118] Adenomyosis is defined as intramyometrial presence of endometrial mucosa surrounded by reactive hypertrophic myometrium.[150] The morcellation of the uterus during LSH may be an impediment for a correct histological diagnosis. In addition, a strict definition of adenomyosis regarding dept of invasion criteria for endometrial glands within the myometrium may also cause a low prevalence in our trials.[115;118;147;149;150;155]

A written standardized questionnaire was used for all three trials. Except for the SF-36 questionnaire, the primary examiner was not blinded for the written answers given by the study participants. This method guaranteed to clear up any misinterpretation of the questions. In addition, the primary examiner was blinded for the allocated treatments during most of the questions, both preoperatively and 12 months after hysterectomy. In contrast, this method is vulnerable for evaluation of patient satisfaction after treatment. The primary examiner might have biased study participants when filling out the questionnaires. Therefore, the trials may have improved if we had chosen to blind even more of the questions for the primary examiner at the outpatient clinic.

9.3 Interpretation of the results

The main objective in Paper 1 was to evaluate the long-term effect of removal of the endocervix during laparoscopy with a reverse LEEP-technique using the Lapcone electrode. This device was developed in order to reduce the occurrence of

vaginal bleeding after LSH. The modification of the surgical procedure by excision of the endocervix after amputation of the cervix appeared to have no effect on the occurrence of vaginal bleeding following LSH compared to the traditionally LSH-procedure. In spite of our continued effort to improve outcomes after this procedure, the results in Paper 1 and 3 showed a relatively high occurrence of vaginal bleeding 12 months after LSH. There might be other mechanisms of bleeding after LSH than remnant endometrial tissue in the upper cervical canal. Possible mechanisms could be angiogenesis or regeneration of endometrial tissue in the upper cervical canal. However, all bleeding episodes after LSH were minimal and did not affect patient satisfaction. This confirms the results from a large retrospective trial by Lieng et al.[31]

There was a significant reduction of cyclic pelvic pain following LSH and TLH (Paper 2 and 3). We found no difference in reduction of cyclic pelvic pain 12 months after TLH and LSH, respectively. This result is supported by a previous RCT that compared these two procedures. In this trial by Morelli et al, written in Italian, all study participants experienced a reduction in symptoms of pelvic and back pain, but there were no differences between the two allocated treatments groups during two years follow-up.[79] Another RCT by Flory et al compared outcomes after LSH and LAVH, respectively.[78] They found a great reduction in pain but no significant differences between the allocated treatments were identified six months after surgery. The main controversy is to perform LSH in women with a high degree of dysmenorrhea or suspected endometriosis and/or adenomyosis. Previous studies have demonstrated the risk of pelvic pain after LSH, but none of these trials had an adequate control group.[31;95;96;107] Both Paper 2 and 3 demonstrated an equal reduction of cyclic pelvic pain after LSH for both women with and without endometriosis and adenomyosis. In addition, there was no difference between outcomes after TLH and LSH when these conditions were compared. Although the number of women included in these analysis is low, these results support the view of gynecologists who claim that LSH is an adequate procedure for women suffering from benign disorders, regardless of the occurrence of cyclic pelvic pain, endometriosis and/or adenomyosis. To secure a long-term pain relief and effective treatment of endometriosis, all endometriosis must be removed during hysterectomy. The cervix shall only be preserved in cases where

this is possible. Furthermore, the results in this trial cannot be adapted to women suffering from severe or deep infiltrating endometriosis, as these conditions were not included in the trial. Unfortunately, there is a lack of other studies of women with pelvic pain, endometriosis and adenomyosis comparing outcomes after different methods of MIS hysterectomy.

Hysterectomy performed because of benign conditions is usually associated with improvement in Qol and high patient satisfaction, especially if the surgical method has a low re-admission and complication-rate.[5;22;29;31;35;40-42;64;73;78;79;90;156-161] The trials in this PhD thesis confirmed this general impression of a high patient satisfaction and improved Qol after both LSH and TLH, respectively. There is a shortage of additional RCTs comparing clinical outcomes following different methods of MIS hysterectomies. In contrast, several RCT`s have evaluated outcomes after traditional SAH and TAH, respectively.[14;17-19;23;24;76;77;82;83] Even at nine-year follow up after the procedures, Thakar et al found no long-term differences between these two procedures.[83] Therefore, the cervix might not play an important role in outcomes after hysterectomy.

In the Lap-hyst-trial, there was a shorter procedure time for LSH compared to TLH. In addition, a tendency of faster recovery, less re-consultations and complications after LSH compared to TLH was documented. This confirms results from larger retrospective and prospective non-randomised trials.[28-30;33;33;35;40;41;63;73;87-91;105;162] In large gynecological departments, the incidence of vaginal cuff dehiscence after TLH is reported to be $< 1\%$.[29;33;163;164] Unfortunately, two women (6.5%) experienced this complication in the Lap-Hyst-trial. To thoroughly explore complications after TLH and LSH, larger studies must be conducted. Especially, this is the case when rare complications like urethral injuries or morcellating of sarcomas in anticipated benign conditions are explored.[29;33;162] Infrequent complications are mainly detectable in large population-based-trials or national registers.[10] Therefore, the trials included in this PhD thesis cannot strongly conclude regarding difference in complications between the assigned treatments.

10. CONCLUSIONS AND PERSPECTIVES

10.1 Conclusions

1. The excision of the endocervix by a reverse conisation during LSH appears to have no effect in terms of reduced bleeding after the procedure compared to the standard LSH-technique. Episodes of vaginal bleeding after LSH are relatively common. All bleeding episodes after LSH are minor and do not seem to affect patient satisfaction. Is it important to inform women of the risk of vaginal bleeding after this procedure, preoperatively. Women who are treated with LSH must accept the risk of minimal vaginal bleeding after the procedure. If feasible, women who do not accept episodes of vaginal bleeding after hysterectomy should be offered VH or TLH.

2. There is no difference in occurrence, intensity or reduction of cyclic pelvic pain 12 months after TLH compared to following LSH. The cyclic pelvic pain is reduced to a minimum 12 months after LSH and TLH, respectively. In addition, this relief of pain also occur for women with minimal, mild or moderate endometriosis detected and treated during the procedure and for women with adenomyosis confirmed in the specimen after hysterectomy. There seems to be no difference in reduction of cyclic pelvic pain in women with or without perioperative detection of minimal, mild or moderate endometriosis and for women with or without histological confirmed adenomyosis.

3. Patient satisfaction after LSH and TLH is very high. There is a significant improvement in Qol 12 months after both procedures. There are no differences between TLH and LSH in the outcomes of patient satisfaction and Qol 12 months after the procedures.

10.2 Perspectives

The trials included in this PhD thesis revealed no differences in cyclic pelvic pain, patient satisfaction and Qol 12 months after TLH and LSH, respectively. Therefore, both procedures should be considered equally successful. The LSH-procedure has comparable results for women with a high degree of dysmenorrhea, endometriosis or adenomyosis compared to TLH. The safest surgical method should be preferred, if there are no documented differences in the essential outcomes of benign conditions. To evaluate the benefits and risks of the alternative surgical treatment options, an individual risk analysis should be presented to the women, preoperatively.

In spite of the current recommendations of using MIS in hysterectomy for benign conditions, AH continues to be a frequently used method. Vaginal hysterectomy is a preferred option, but this method has some limitations. The TLH-technique requires more advanced skills for laparoscopic dissection and suturing compared to LSH. Therefore, to safely accomplish a total hysterectomy in women with fibroids, TAH might be the only manageable technique for many gynecologists. Consequently, to avoid laparotomy in such cases, the gynecologist should consider performing LSH. A more extent use of LSH may be an important contribution to reduce abdominal hysterectomy and fully implement minimal invasive hysterectomy worldwide.

Some challenges and limitations of MIS hysterectomy in benign conditions need to be assessed in future studies. There should be a continued focus of reducing complications, adverse events and morbidity of the treatment. To address this problem properly, there should be a mandatory national register of hysterectomy and laparoscopic procedures. In such a register, methods and equipment used must be registered. At current date, the Norwegian Society for Gynaecology and Obstetrics has a voluntary register for endoscopic gynaecological surgery.[165] On the basis of the current evidence regarding methods of hysterectomy, I recommend the Norwegian Board of Health Supervision to make this register compulsory for all hysterectomies performed in Norway.

Furthermore, at current date there are no perfect methods for tissue extraction during LSH. Gynecologists should work to improve the method for a safe and practical way to extract the specimen during LSH.

Although bleeding after LSH does not seem to affect patient satisfaction, gynecologists should be encouraged to improve the method of LSH in order to avoid unnecessary bleeding episodes after the procedure. There are several possible mechanisms for bleeding after LSH that needs to be clarified.

11. ERRATA

12. REFERENCES

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11. PAPERS I-III

I

II

III

Pain reduction after total laparoscopic hysterectomy and laparoscopic supracervical hysterectomy among women with dysmenorrhea: a randomised controlled trial

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Running title: Pelvic pain after TLH and LSH, a randomised controlled trial

Abstract

Objective: To compare reduction of cyclic pelvic pain, patient satisfaction and quality of life (Qol) after total laparoscopic hysterectomy (TLH) and laparoscopic supracervical hysterectomy (LSH) in premenopausal women suffering from dysmenorrhea.

Design: Randomised blinded controlled trial.

Setting: Norwegian university teaching hospital.

Sample: Sixty-two women with dysmenorrhea on a basis of a benign condition.

Methods: The study participants were randomised to either TLH (n = 31) or LSH (n= 31).

Main outcome measures: The main outcome measure was reduction of cyclic pelvic pain 12 months after hysterectomy measured by a visual analogue scale (VAS), range 0-10. Secondary outcome measures were patient satisfaction (VAS, range 0-10) and Qol (Short Form 36, range 0-100).

Results: The mean preoperative cyclic pelvic pain in the two treatment groups of TLH and LSH was 6.6 (2.4) and 6.8 (2.0), respectively (p=0.70). The mean reduction of this pain 12 months after TLH was 5.8 (SD 2.6) compared to 6.0 (SD 2.6) after LSH, p=0.77. The mean patient satisfaction was 9.3 (1.5) and 9.1 (SD 1.2) 12 months after TLH and LSH, respectively (p=0.66). The Qol improved in both allocated treatment groups 12 months after hysterectomy, p<0.01. The mean Qol-score 12 months after TLH and LSH was 81.6 (SD 17.8) and 80.2 (SD 18.0), respectively (p=0.56).

Conclusion: The reduction of cyclic pelvic pain 12 months after TLH and LSH were comparable. The study participants in the two allocated treatment groups had a similar improvement in Qol and seemed to be equally satisfied with the treatment 12 months after the procedures.

Keywords: Cervical stump symptoms; Cyclic pelvic pain; Dysmenorrhoea, Laparoscopic hysterectomy; Laparoscopic supracervical hysterectomy; Patient satisfaction; Pelvic pain; Quality of life; Randomised controlled trial; Total laparoscopic hysterectomy.

Clinical Trial Registration

ClinicalTrials.gov February 9th 2011, identifier: NCT01289314.

Introduction

The technique for hysterectomy has been debated throughout the last century. The controversies have mostly been related to diversity in surgical approach and removal of the cervix in women with benign gynecological disorders.[1-15] When performing hysterectomy, there is an indisputable recommendation to avoid laparotomy by using minimal invasive surgery (MIS) techniques.[16-18] If vaginal hysterectomy is not feasible the laparoscopic approach is recommend.[16-18] Most hysterectomies include removal of the cervix, but the rate of subtotal hysterectomy in women with benign conditions requiring hysterectomy has increased.[19-30] Laparoscopic supracervical hysterectomy (LSH) has for the last decade been the preferred method for hysterectomy in selected cases at our hospital.[26;31-36] We perform this procedure in premenopausal women with benign conditions and no history of previous cervical dysplasia. LSH is associated with high patient satisfaction. The LSH-technique demands less advanced skills for laparoscopic dissection and suturing, ensures a faster recovery after surgery and a lower risk of perioperative complications compared to total laparoscopic hysterectomy (TLH) and laparoscopically assisted vaginal hysterectomy (LAVH).[22;29;37-44] However, leaving the cervix is debatable.[13;16;17;19;31;32;35;43;45-52] A risk of persistent pain and repeated surgery after LSH has been documented.[30;32;50;51;53;54] Consequently, many authors have stated that supracervical hysterectomy should not be performed in women with endometriosis, pelvic pain or dysmenorrhea.[3;30;50;51;54] In contrast, other gynaecologists conclude that endometriosis or pelvic pain should not be contraindications for performing LSH, unless leaving the cervix compromises the removal of endometriosis.[32;40;55;56]

The main objectives of surgical treatment in patients who suffer from benign conditions are through a safe method to eradicate or reduce symptoms and improve quality of life (Qol). Therefore, when outcomes of hysterectomy are studied in benign gynaecological

conditions it is vital to evaluate patient satisfaction and Qol. Short Form 36 (SF-36) is a validated and well-documented questionnaire for this purpose.[57] The literature of outcomes following MIS hysterectomies mainly consists of case series and retrospective reports.[9;18;19;30;48] Consequently, there is a need for randomised controlled trials (RCT) that compare long-term clinical outcomes after these procedures. The persistent controversies regarding methods of MIS hysterectomies encouraged us to carry out this blinded RCT. The objective of this trial was to compare reduction of pelvic pain, patient satisfaction and Qol 12 months after TLH and LSH, respectively.

Methods

This was a blinded, single centre RCT, performed in a Norwegian university hospital. The 0-hypothesis of the trial was: there is no significant difference in reduction of cyclic pelvic pain following TLH compared with following LSH. The study was conducted in accordance with the Declaration of Helsinki and national as well as local regulations. The Scientific Advisory Board at Oslo University Hospital (OUS), the Advisory Committee on the Protection of Patient Records at OUS and the Regional Committee for Medical Research Ethics in eastern and southern Norway approved the trial and the study was registered in ClinicalTrials.gov before recruiting study participants.[58]

The women were invited to participate and enrolled in the trial at the outpatient clinic. Premenopausal women referred to the Department of gynaecology, OUS due to a benign condition requiring hysterectomy were eligible for study recruitment. The trial included women with preoperative cyclic pelvic pain, defined as premenstrual or dysmenorrhoeal pain. The exclusion criteria were women unable to communicate in Norwegian language, previous history of cervical dysplasia, cellular changes suggestive of cervical dysplasia or malignancy in preoperative cervical smear or atypical hyperplasia or malignancy in endometrial biopsy. In addition, women with a substantially enlarged uterus were excluded. This was defined as

corpus uteri measured by transvaginal ultrasound of more than 10 or 12 centimetres in anterior-posterior or transversal diameter, respectively. Furthermore, women with occurrence of pelvic organ prolapse (POP) more than grade 1, menopausal women, women with a concomitant condition requiring removal of both ovaries or with preoperative symptoms dominated by a non-cyclic chronical pelvic pain and preoperative signs of severe or deep infiltrating endometriosis were not included in the trial.[59-62] The preoperative classification of severe endometriosis was defined as presence of large endometriomas, suspected extensive adhesions or kissing ovaries due to endometriosis. Consequently, peritoneal endometriosis or endometriosis in the pouch of Douglas was not a contraindication of being included in the trial, unless leaving the cervix compromised the removal or destruction of endometriosis. Endometriosis diagnosed perioperatively was treated during the procedure by electrocoagulation or excision.

The authors of the study were primarily responsible for recruiting women. A study nurse, not otherwise involved in the trial, performed the randomization procedure, using the randomization plan generator with permuted blocks.[63] The study participants were randomised to either TLH (n = 31) or LSH (n = 31). The assigned treatment was concealed in numbered envelopes stored in the operating theatre. All recruited women were numbered consecutively corresponding to the numbered envelopes. The envelope was not opened until general narcosis of the study participant was established. In order to increase the validity of the trial, the assigned procedure was blinded for the study participants throughout the follow-up period. The women and the primary examiner (the first author) were informed of allocated treatment after completing the study forms at follow-up 12 months after the procedure. If major complications occurred, the study participants and primary examiner were informed of the allocated treatment at the time of suspected complication.

The study participants underwent hysterectomy under general intravenous anaesthetic. Six experienced endoscopic gynaecologists with assistance from residents performed the procedures. All procedures were performed using 10-millimeter 30-degree laparoscopic cameras. The Pelosi Mobiliser and Vcare® uterine manipulator by ConMed Endosurgery, Utica, NY, United States, were used during LSH and TLH, respectively. The LSH was performed in accordance with the standardised operative technique at our department.[35] During TLH, the surgeons individually determined the method and suture for vaginal cuff closure. This was either performed by a continuous suture of 0 (3.5 Metric) V-loc™ 180 absorbable polyglyconated or cross-sutures of 0-Polysorb, manufactured by Covidien, Dublin, Ireland. All study participants received 1500-milligram of metronidazole and 400-milligram doxycycline intravenously during the procedure as a single dose of prophylactic antibiotics. The study participants were scheduled for one night admittance before they were discharged from the hospital. They were prescribed and recommend taking a sick leave for 18-20 days after the procedure. They were advised to avoid sexual intercourse the first eight weeks following surgery. If study participants had suspicion of any complications after discharge from the hospital, they were informed to contact the department of gynaecology, directly.

The study participants and the primary study examiner registered most of the outcome measures at the outpatient clinic preoperatively and at follow-up 12 months after surgery. A written standardised questionnaire was used. Some outcome measures were reported through a standardised clinical interview and examination completed by the primary examiner.

The primary outcome in this the trial was reduction of cyclic pelvic pain 12 months after the procedures measured by a visual analogue scale (VAS) with the range 0-10. The occurrence and intensity of cyclic pelvic pain was also registered in a four-graded ordinal scale (no pain, mild pain, moderate pain or severe pain). After hysterectomy, the cyclic pelvic pain was defined as cyclic pelvic pain with or without concomitant vaginal bleeding. Non-

cyclic pelvic pain was also registered. We used the SF-36 to evaluate Qol.[57] Other variables registered both preoperative and 12 months after surgery were: amount and type of bleeding (cyclic or irregular) measured by VAS (range 0-10) and a five graded ordinal scale, occurrence and grade of POP defined by Pelvic Organ Prolapse-Quantification (POP-Q).[61] Further preoperative variables were age, body mass index (BMI), number of previous births, indication for hysterectomy, any previous pelvic or abdominal surgery including caesarean section, use of Levonorgestrel-releasing intrauterine system (Mirena®), any medication or other medical conditions and uterine size measured by transvaginal ultrasound (anterior-posterior diameter and width of corpus uteri). Additional variables 12 months after hysterectomy were patient satisfaction measured by VAS (range 0-10) and a five graded ordinal scale (dissatisfied, somewhat dissatisfied, neutral, satisfied, very satisfied), return to normal activity (days) and any new symptoms. A scrub-nurse recorded the perioperative variables (operation time, weight of specimen, perioperative complications and estimated blood loss). A nurse at the gynaecological ward registered body temperature, haemoglobin (Hb) preoperatively and one day after surgery, length of stay and eventual complications before discharge from the hospital. All further contacts (re-consultations and readmissions) and minor complications during the 12-month follow-up were registered without disclosing the allocated treatment to study participants.

Cervical cytology and endometrial biopsy preoperatively, histological analysis of specimen from the surgical procedure and cervical or vaginal cytology 12 months after surgery were registered in the trial after study participants had completed outcomes at follow up. A dedicated pathologist analyzed all specimens from the hysterectomies. A cut-off of 2.0 millimetres dept of invasion of endometrial glands below the basalis layer was used as diagnostic criteria for adenomyosis.[64-67] To explore potential menopause, the serum levels of Oestradiol (E2), Follicle Stimulating Hormone (FSH), Lutein hormone (LH) and anti-

Mullerian hormone (AMH) were analyzed preoperatively and 12 months after hysterectomy. Women lost to follow-up 12 months after hysterectomy were contacted by phone and received a letter with a request to have the follow-up consultation together with a second appointment for such a consultation.

The expected mean pain reduction in the LSH group was 3.3 (SD 2.7).[35] During planning of the trial, there was no available data for the expected reduction of pain after TLH. A difference in pain reduction equal to 1 SD was considered to be of clinical importance. The test power and level of significance in the trial were set to 90 % and 0.05, respectively. Consequently, 62 women were required in the trial. All data were analyzed using SPSS 18.0 (SPSS Inc., Chicago, IL). Normally distributed continuous data from two study groups were analyzed using a two-sided Independent Samples Student t-test and the Paired Samples t-test when paired and categorical data were analyzed using Pearson Chi-Square. The Mann-Whitney U test or Wilcoxon Signed Rank Test were used for non-normally distributed data. All analyses were performed and reported according to the principle of intention to treat. The trial was conducted according to the CONSORT guidelines.[68;69]

Results

The study participants were included and treated from February 2011 to November 2012, figure 1. Hysterectomy was not performed in one woman due to other medical reasons. Therefore, 61 women received the allocated treatment. The demographic variables and intensity of cyclic pelvic pain were equal for the two allocated treatment groups preoperatively, table 1. Women lost to follow-up (n=3) did not differ from other study participants in demographic characteristics or preoperative cyclic pelvic pain. The main indications for hysterectomy were fibroids, dysmenorrhea and abnormal uterine bleeding in 39 (62.9 %), 14 (22.6 %) and 9 (14.5 %) women, respectively. The perioperative variables and histological diagnosis of specimen are shown in table 2. The mean weight of specimens

was 187.3 (SD 93.7) grams. LSH had a shorter duration of surgery compared to TLH, p<0.01. Endometriosis was equally detected (n=15, 24.6 %) in both allocated treatment groups during the surgical procedures. The pathologist diagnosed fibroids and adenomyosis in 49 (80.3 %) and 27 (44.3 %) of the specimen, respectively, and 20 women had both conditions.

There was an equally distribution in severity of cyclic pelvic pain between the allocated treatment groups, preoperatively (p=0.69). In total, 28 (90.3%) study participants in the TLH- and LSH-group reported the preoperative pain to be moderate or severe. The intensity of cyclic pelvic pain was reduced 12 months after hysterectomy, p<0.01 (Table 3). The mean reduction of cyclic pelvic pain 12 months after TLH and LSH was 5.8 (SD 2.6) and 6.0 (2.4) measured by VAS, respectively (p= 0.77). The occurrence of cyclic pelvic pain in both allocated treatment groups was reduced to a minimum 12 months after the procedures, p<0.01. Consequently, 42 (71.2 %) and 12 (20.3 %) study participants experienced no pain or only mild pelvic pain 12 months after the procedures, respectively. In total, reported 10 (32.3 %) women cyclic pelvic pain 12 months after TLH compared to 7 (25.0 %) women after LSH, p=0.54.

Except for one woman, all study participants were very satisfied (n=51) or satisfied (n=7) with the treatment 12 months after hysterectomy. There was no difference in patient satisfaction between the two allocated treatment groups 12 months after the procedures, p=0.66. The patient satisfaction after TLH and LSH was 9.3 (SD 1.5) and 9.1 (SD 1.2) measured by VAS, respectively. Women experiencing cyclic pelvic pain 12 months after LSH (n=7) had a lower patient satisfaction compared to women with no pelvic pain (n=21), p=0.02. The mean patient satisfaction VAS scores for these two subgroups were 8.0 (SD 1.8) and 9.5 (SD 0.7), respectively. The corresponding patient satisfaction VAS scores in women with (n=10) or without (n=21) occurrence of cyclic pelvic pain 12 after TLH were and 9.3 (SD 0.6) and 9.3 (SD 1.7), respectively (p=0.88).

The mean Qol scores 12 months after hysterectomy measured by SF-36 were higher compared to the preoperative values for all study participants and for both allocated treatment groups, $p<0.02$. This improvement of Qol scores were confirmed in all eight subgroups of SF-36, $p<0.05$. No difference in total Qol-score between TLH and LSH 12 months after the procedures was detected, $p=0.43$.

Furthermore, there were no differences between the two allocated treatment groups in pelvic pain reduction, patient satisfaction or Qol 12 months after hysterectomy for women with or without endometriosis and for women with or without adenomyosis, respectively (table 4). Study participants with endometriosis detect during surgery reported the same intensity of preoperative cyclic pelvic pain compared to women without endometriosis, $p = 0.89$. The mean reduction of cyclic pelvic pain by VAS for women with and without endometriosis 12 months after hysterectomy was 5.8 (SD 2.2) and 5.9 (SD 2.6), respectively. In contrast, study participants with adenomyosis reported higher preoperative cyclic pelvic pain (mean 7.7, SD 1.6) compared to women without this diagnosis (mean 6.0, SD 2.4), $p=0.03$. There was a tendency of a greater pelvic pain reduction in women with adenomyosis (mean 6.5, SD 2.3) compared to women without this diagnosis (mean 5.3, SD 2.6), $p=0.06$. The mean patient satisfaction 12 months after hysterectomy for women with or without endometriosis was 9.2 (SD 0.6) and 9.2 (SD 1.5), respectively ($p=0.99$). The corresponding figures for women with or without adenomyosis were 9.1 (SD 1.7) and 9.3 (SD 0.9), respectively ($p=0.55$).

No perioperative complications occurred and the perioperative blood loss was negligible for all procedures in the trial. Therefore, no difference in blood loss between the two treatment groups was detected. The reduction in Hb from the preoperative value compared to one day after the procedure was 1.4 (1.0) and 1.4 (0.7) for TLH and LSH, respectively ($p=0.87$). All women stayed for one night in hospital after hysterectomy, except

for two women who left the hospital just a few hours after LSH. The women returned to normal activity after LSH and TLH within mean 25.8 (SD 11.9) and 35.8 (SD 26.8) days, respectively (p=0.15). We found a trend of more re-consultations after discharge from the hospital in the TLH-group (n=11), compared to the women who were treated with LSH (n=5), p=0.08. In total, six complications were registered during the trial period. There were 5 (16.1 %) complications subsequent to TLH compared to 1 (3.3 %) after LSH, p=0.11. Three lower urinary tract infections were diagnosed and treated within the first month after TLH. In addition, three major complications occurred. One woman was diagnosed with an infected cervical top hematoma three weeks after LSH. She was readmitted to the hospital and successfully treated with antibiotics intravenously. Two women experienced vaginal dehiscence three and six months after TLH, respectively. They were both re-operated with laparoscopic suture of the vaginal cuff. All three women who suffered from major complications were informed about their allocated treatment at the time of suspected complication. At 12 months follow-up, they all scored high patient satisfaction, had no cyclic pelvic pain and a great improvement in Qol-scores. As expected, we found a higher occurrence of vaginal bleeding after LSH compared to TLH, p=0.05. In the LSH group, four (14.3%) women had regular and five (17.9%) irregular bleeding, respectively. In the TLH group, three (9.7%) women reported irregular vaginal bleeding episodes after the procedure and additional two were diagnosed with a non-bleeding granulating polyp in the vaginal top. The occurrence of vaginal bleeding did neither affect patient satisfaction nor Qol 12 months after hysterectomy. There was an equal distribution of preoperative asymptomatic grade 1 POP in the TLH- and LSH-group, (p=0.72). This incidence was 5 (16.1%) and 4 (13.3%) in each allocated treatment group, respectably. There was a higher incidence of asymptomatic grade 1 POP 12 months after TLH (n=10, 32.3%) compared to preoperatively, p=0.03. This increase was not found in the LSH-group, as only 5 (17.8%) POP’s were documented 12

months after surgery. In addition, no difference between the two allocated treatment groups was detected comparing values of FSH, LH, E2 and AMH preoperatively and 12 months after hysterectomy. In total, there was a higher level of FSH and LH detected 12 months after hysterectomy compared the preoperative values (p=0.02). No comparable changes in E2 and AMH were detected.

Discussion

Main Findings

The main result in this trial was that we found no difference in reduction of cyclic pelvic pain 12 months after TLH and LSH. In addition, there were no differences in cyclic pelvic pain, patient satisfaction or Qol between the two allocated treatment groups 12 months after the procedures. The outcomes subsequent to TLH and LSH were comparable for women with or without endometriosis and for women with or without adenomyosis. There was a shorter duration of surgery for LSH compared to TLH. In addition, there was a tendency of more re-consultations, complications and POP's following TLH compared to after LSH.

Strengths and Limitations

A strong external validity for the primary outcome was taken care of by the methodological strength of this blinded RCT. The main weakness of this trial is the number of study participants, which limits conclusions beyond the main outcome. Consequently, results of subgroup analysis such as clinical outcomes in women with endometriosis and adenomyosis in the trial must be interpreted with caution. The prevalence of endometriosis and adenomyosis is reported in a wide range (20-60 %) in different studies of hysterectomy.[66;67;70] We diagnosed these conditions in 24.6 % and 44.3 % of the study participants, respectively. If this trial should have been powered for sub-group analysis of endometriosis and adenomyosis, a pilot study and additional power analysis should have been performed before study start.

In addition, the trial had most likely improved if we had used a validated endometriosis-scale.[59;60;62] Unfortunately, these scales were not systematically in use at our department at the time we planned and conducted the trial. Furthermore, the results in this trial cannot be adapted in severe or deep infiltrating endometriosis, as these conditions were not included in the trial.

Interpretation

The main outcome of our trial is supported by a previous RCT written in Italian comparing these two procedures.[71] Morelli et al randomised 141 women to either TLH or LSH. They found no statistical differences between the two allocated treatments groups at two years follow-up. In total, experienced 14 (20 %) women pelvic pain 12 months after TLH compared to 16 (22 %) after LSH, p=0.71. A complementary RCT has compared LSH with a MIS procedure that resembles TLH; the laparoscopically-assisted vaginal hysterectomy (LAVH).[72] In this trial, Flory et al detected a great reduction in pain, improvement of symptoms and psychosocial outcomes six months after the procedures, but no significant differences between LAVH (n=32) and LSH (n=31) were identified.

To perform a large high-quality RCT comparing different methods of hysterectomies is costly, time-consuming and therefore rarely conducted.[4;6;9;15;71-78] Consequently, there is a shortage of additional RCTs comparing methods of MIS hysterectomies.[4;9;19;30] A large prospective non-randomized trial by Wellwiener et al (n=1952) has reported results in favour of LSH in peri- and postoperative outcomes and complication compared to TLH (Wellwiener 2013).[43] This trial is similar with our trial in preoperative demographic, clinical characteristics and surgical data. A supplementary prospective non-randomised trial by Einarsson et al (n=122) has demonstrated a greater improvement in short-term postoperative Qol after LSH compared to TLH measured by SF-36.[22] In addition, this trial demonstrated a similar result as our trial of more complications and readmissions after TLH compared to LSH. Several RCT`s

have evaluated outcomes after traditional supracervical (SCH) or total abdominal hysterectomy (TAH), respectively.[6;15;28;73;75-78] Even at nine-year follow up after the procedures, Thakar et al found no long-term differences between TAH and SCH.[78]

Our trial reflects on whether it is acceptable to perform LSH in women with a high degree of dysmenorrhea or suspected endometriosis and/or adenomyosis. Although the sample size in our study is small, the results indicate that women with cyclic pelvic pain and endometriosis and/or adenomyosis achieve symptom relief and improved Qol regardless of whether the cervix is removed or not. The result supports findings from an additional observational trial from our department.[32] This trial, demonstrated a reduction of cyclic pelvic pain 12 months after LSH, including for the women with endometriosis or adenomyosis. It is important to emphasize that all endometriosis must be removed together with the hysterectomy to secure a long-term pain relief and effective treatment of endometriosis. The cervix shall only be preserved in cases where this is possible. Furthermore, several retrospective studies have demonstrated a risk of pelvic pain after LSH, but none of these trials had representative control groups.[32;35;50;51;54] Unfortunately, there is a lack of other prospective studies including women with pelvic pain, endometriosis and adenomyosis comparing outcomes after different methods of hysterectomies.[9;19;66]

Conclusion

In this RCT we found no differences in long-term outcomes of cyclic pelvic pain, patient satisfaction and Qol 12 months after TLH compared to LSH. If there are no documented differences in the essential outcomes, the safest surgical method should be preferred. LSH is fairly easy to accomplish with a lower risk of major complications compared to TLH. Consequently, LSH should be a recommended approach for MIS hysterectomy in selected cases of women suffering from dysmenorrhea.

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Disclosure statement

The authors report no conflict of interest.

Contribution to Authorship

The contribution of each author is as follows: EB contributed by planning the study, collecting data, performing the statistical analyses and interpretation, writing and revising the manuscript and final approval of the submitted manuscript. EQ contributed by planning the study, interpretation of statistical analysis, writing and critical revision of the manuscript, and final approval of the submitted manuscript. KM: contributed by planning the study, analyzed the specimens from operation, writing and critical revision of the manuscript, and final approval of the submitted manuscript. ML contributed by designing, facilitating and planning the study, collecting data, performing the statistical analyses and interpretation, writing and revising the manuscript, and final approval of the submitted manuscript.

Details of Ethics Approval

The Regional Committee for Medical Research Ethics in eastern and southern Norway approved the study protocol January 6th 2011, reference number 2010/3020.

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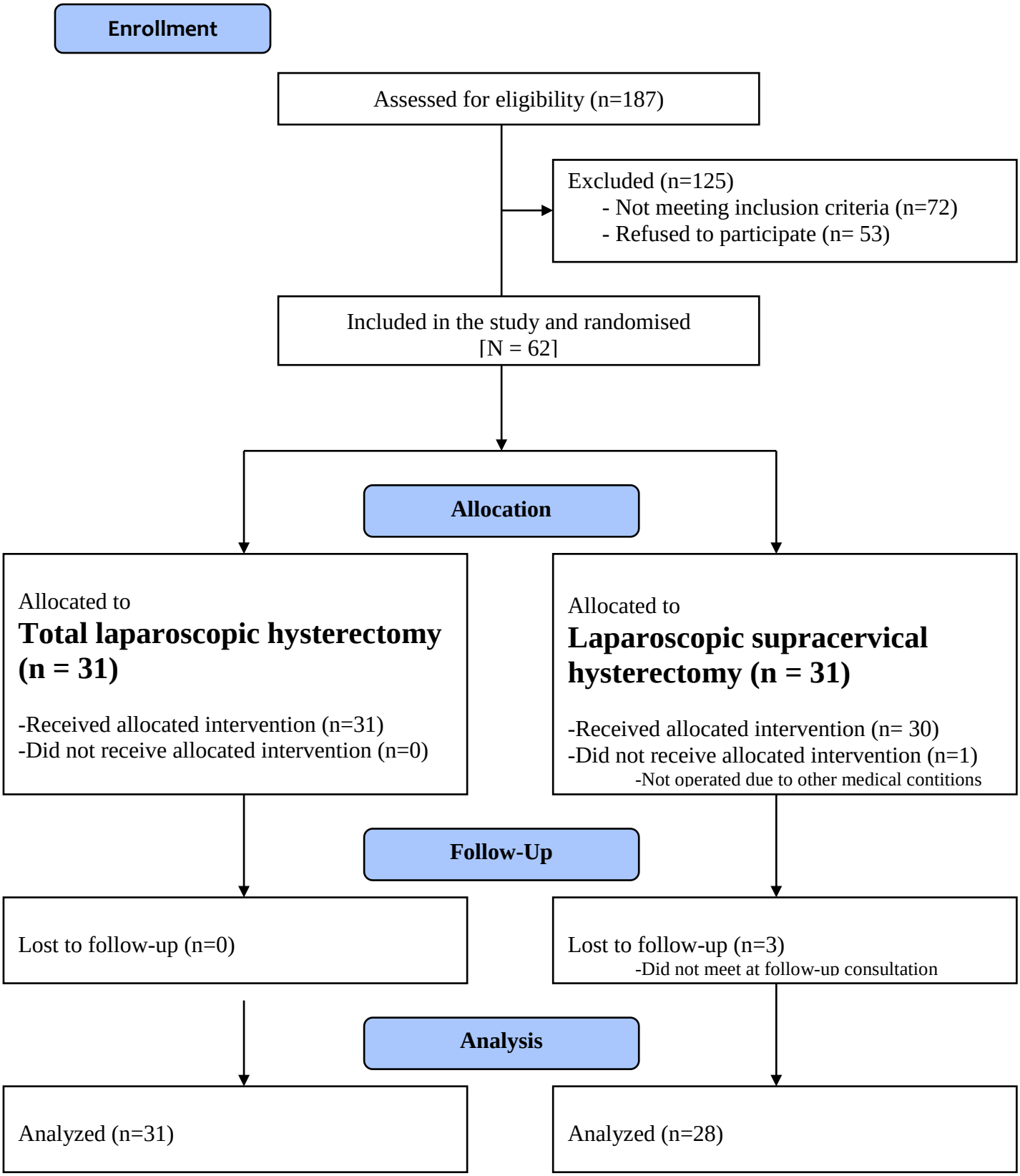
Enrollment
Assessed for eligibility (n=187)
Excluded (n=125)
- Not meeting inclusion criteria (n=72)
- Refused to participate (n= 53)
Included in the study and randomised
[N = 62]
Allocation
Allocated to
Total laparoscopic hysterectomy (n = 31)
-Received allocated intervention (n=31)
-Did not receive allocated intervention (n=0)
Allocated to
Laparoscopic supracervical hysterectomy (n = 31)
-Received allocated intervention (n= 30)
-Did not receive allocated intervention (n=1)
-Not operated due to other medical contitions
Follow-Up
Lost to follow-up (n=0)
Lost to follow-up (n=3)
-Did not meet at follow-up consultation
Analysis
Analyzed (n=31)
Analyzed (n=28)

Table 1: The preoperative demographic data, cyclic pelvic pain and quality of life in the two allocated treatment groups.

	TLH[1] (n=31)	**LSH[2] (n=31)**	**p-value**
Age (years), mean (SD)	45.1 (5.6)	44.5 (4.2)	0.62
Body mass index, mean (SD)	26.0 (6.1)	26.3 (5.1)	0.78
Smoking, n (%)	10 (32.3)	14 (45.2)	0.55
Number of births, median (range)	1 (0-4)	1 (0-4)	0.52
Previous caesarean delivery, n (%)	5 (16.1)	7 (22.6)	0.50
Previous operations score, median (range)[3]	1 (0-4)	1 (0-5)	0.84
Previous hysteroscopic resection, n (%)[4]	7 (22.6)	6 (19.4)	0.76
Use of LNG-IUS, n (%)[5]	5 (16.1)	6 (19.4)	0.74
Fibroids detected preoperatively, n (%)[6]	27 (87.1)	22 (71.0)	0.21
Fibroids, largest diameter (cm), mean (SD)[6]	3.4 (1.3)	4.2 (1.6)	0.42
Anterior-posterior diameter of corpus uteri, mean (SD)[6]	5.7 (1.2)	6.0 (1.3)	0.30
Transversal diameter of corpus uteri, mean (SD)[6]	6.7 (1.0)	7.0 (1.5)	0.30
Pelvic organ prolapse grade 1, n (%)[7]	5 (16.1)	4 (13.3)	0.72
Vaginal bleeding (VAS), mean (SD)[8]	7.4 (2.1)	8.4 (1.4)	0.02
Cyclic pelvic pain (VAS), mean (SD)[8]	6.6 (2.4)	6.8 (2.0)	0.70
Quality of life (SF-36, total score), mean (SD)[9]	64.0 (17.4)	66.3 (21.6)	0.56

[1] Total laparoscopic hysterectomy (TLH).
[2] Laparoscopic supracervical hysterectomy (LSH).
[3] Previous operations score, measured by a total score:
1 point for each previous laparoscopy and 2 points for each previous laparotomy including caesarean sections.
[4] Hysteroscopic endometrial resection or resection of fibroids.
[5] Levonorgestrel-releasing intrauterine system (LNG-IUS), Mirena®.
[6] Measured by vaginal ultrasound.
[7] Pelvic organ prolapse (POP) grade 1, POP-Quantification (POP-Q).
[8] Visual analogue scale (VAS), range 0-10.
[9] Short form 36 (SF-36), Range 0-100. A total score is reported when all questions of SF-36 are completed.
This score is reported in allocated groups of TLH (n=29) and LSH (n=31), respectively.

Table 2: Perioperative variables and histological diagnosis of specimen from hysterectomy in the two allocated treatment groups.

	TLH[1] (n=31)	**LSH[2] (n=30)**	**p-value**
Duration of surgery (minutes), mean (SD)[3]	102.7 (27.3)	76.0 (25.1)	< 0.01
Weight of specimen (gram), mean (SD)	180.2 (68.6)	194.1(114.8)	0.56
Haemoglobin drop (g/dL), mean (SD)[4]	1.4 (1.0)	1.4 (0.7)	0.87
Endometriosis detected during surgery, n (%)[5]	7 (22.6)	8 (26.7)	0.47
Histology sections examined per specimen, mean (SD)	6.2 (2.6)	5.3 (1.0)	0.11
Adenomyosis in specimen, n (%)	15 (48.4)	12 (40.0)	0.51
Fibroids in specimen, n (%)	26 (83.9)	23 (76.7)	0.35

[1] Total laparoscopic hysterectomy (TLH)
[2] Laparoscopic supracervical hysterectomy (LSH)
[3] Time from application of the uterine manipulator until completed skin closure.
[4] Difference in Hemoglobin, preoperative value compared to one day after surgery.
For two women in the LSH-group, the postoperative value was measured the before discharge day of surgery.
[5] Endometriosis diagnosed during surgery was treated during the procedure by electrocoagulation or excision.

Table 3: Outcome measures in the allocated treatment groups 12 months after hysterectomy

	TLH[1] (n=31)	**LSH[2] (n=28)**	**p-value**
Cyclic pelvic pain reduction (VAS), mean (SD)[3,4]	5.8 (2.6)	6.0 (2.6)	0.94
Cyclic pelvic pain 12 months after hysterectomy (VAS), mean (SD)[3]	0.8 (1.6)	0.8 (2.0)	0.77
Cyclic pelvic pain 12 months after hysterectomy, n (%)	10 (32.3)	7 (25.0)	0.54
Patient satisfaction 12 months after hysterectomy, mean VAS (SD)[3]	9.3 (1.5)	9.1 (1.2)	0.43
Qol 12 months after hysterectomy (SF-36, total score), mean (SD)[5]	81.6 (17.8)	80.2 (18.0)	0.69
Qol (SF-36, total score) improvement, mean (SD)[5,6]	17.6 (20.0)	13.9 (26.0)	0.56
Pelvic organ prolapse 12 months after hysterectomy, n (%)[7]	10 (32.3)	5 (17.8)	0.23
Occurrence of vaginal bleeding 12 months after hysterectomy, n (%)[8]	3 (9.7)	9 (32.1)	0.03

[1] Total laparoscopic hysterectomy (TLH)
[2] Laparoscopic supracervical hysterectomy (LSH)
[3] Visual analogue scale (VAS), Range 0-10.
[4] Cyclic pelvic pain reduction: Preoperative VAS-score minus VAS-score 12 months after surgery.
[5] Quality of life (Qol) by Short form 36 (SF-36), Range 0-100. A total score is reported when all questions of SF-36 are completed. This score is reported in 29 (93.5 %) and 26 (92.3 %) of the TLH- and LSH-group, respectively.
[6] Qol improvement: SF-36-score 12 months after surgery minus SF-36-score preoperatively.
[7] Pelvic organ prolapse (POP) 12 months after hysterectomy by POP-Quantification, all grade 1.
[8] All bleeding episodes were minor, both cyclic and irregular bleeding reported.
Irregular bleeding episodes reported in the allocated treatment groups: TLH (n=3) and LSH (n=5).

Table 4: Outcome measures 12 months after hysterectomy in the allocated treatment groups for women with and without endometriosis or adenomyosis, respectively.

		TLH[1] (n=31)	LSH[2] (n=30)	p-value
ENDOMETRIOSIS	**No endometriosis detected during surgery, n (%)**	**24 (77.4)**	**22 (73.3)**	**0.71**
	Reduction of cyclic pelvic pain (VAS), mean (SD) [3,4]	5.8 (2.6)	5.9 (2.7)	0.89
	Cyclic pelvic pain (VAS) 12 months after hysterectomy, mean (SD) [3]	0.8 (1.6)	0.8 (2.3)	0.98
	Patient satisfaction (VAS) 12 months after hysterectomy, mean (SD) [3]	9.3 (1.6)	9.2 (1.4)	0.86
	Qol (SF-36, total score) 12 months after hysterectomy, mean (SD)[5]	83.2 (17.2)	82.1 (17.3)	0.82
	Endometriosis detected and treated during surgery, n (%)	**7 (22.6)**	**8 (26.7)**	**0.71**
	Reduction of cyclic pelvic pain (VAS), mean (SD) [3,4]	5.6 (2.8)	6.1 (1.5)	0.71
	Cyclic pelvic pain (VAS) 12 months after hysterectomy, mean (SD) [3]	1.0 (1.5)	0.8 (1.4)	0.82
	Patient satisfaction (VAS) 12 months after hysterectomy, mean (SD) [3]	9.4 (0.5)	9.0 (0.7)	0.26
	Qol (SF-36, total score) 12 months after hysterectomy, mean (SD)[5]	78.8 (20.5)	74.0 (20.2)	0.68
ADENOMYOSIS	**No adenomyosis in specimen from hysterectomy, n (%)**	**16 (51.6)**	**18 (60.0)**	**0.51**
	Reduction of cyclic pelvic pain (VAS), mean (SD) [3,4]	4.9 (2.6)	5.7 (2.6)	0.44
	Cyclic pelvic pain (VAS) 12 months after hysterectomy, mean (SD) [3]	0.5 (1.2)	0.6 (2.1)	0.93
	Patient satisfaction (VAS) 12 months after hysterectomy, mean (SD) [3]	9.5 (0.6)	9.1 (1.1)	0.22
	Qol (SF-36, total score) 12 months after hysterectomy, mean (SD)[5]	83.6 (16.0)	78.6 (17.1)	0.41
	Adenomyosis detected in specimen from hysterectomy, n (%)	**15 (48.4)**	**12 (40.0)**	**0.51**
	Reduction of cyclic pelvic pain (VAS), mean (SD) [3,4]	6.6 (2.4)	6.4 (2.2)	0.74
	Cyclic pelvic pain (VAS) 12 months after hysterectomy, mean (SD) [3]	1.2 (1.8)	1.1 (2.1)	0.94
	Patient satisfaction (VAS) 12 months after hysterectomy, mean (SD)[3]	9.1 (2.0)	9.2 (1.4)	0.88
	Qol (SF-36, total score) 12 months after hysterectomy, mean (SD)[5]	80.6 (20.0)	82.4 (19.6)	0.82

[1] Total laparoscopic hysterectomy (TLH)
[2] Laparoscopic supracervical hysterectomy (LSH)
[3] Visual analogue scale (VAS), Range 0-10.
[4] Cyclic pelvic pain reduction: preoperative VAS-score minus VAS-score 12 months after surgery.
[5] Quality of life (Qol) by Short form 36 (SF-36), Range 0-100. A total score is reported when all questions of SF-36 are completed. This score is reported in 29 (93.5 %) and 26 (92.3 %) of the TLH- and LSH-group, respectively.